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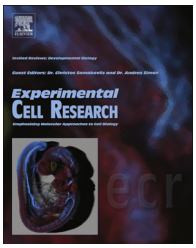

Review Article

Transcriptional regulation and alternative splicing cooperate in muscle fiber-type specification in flies and mammals ☆

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ABSTRACT

Muscles coordinate body movements throughout the animal kingdom. Each skeletal muscle is built of large, multi-nucleated cells, called myofibers, which are classified into several functionally distinct types. The typical fiber-type composition of each muscle arises during development, and in mammals is extensively adjusted in response to postnatal exercise. Understanding how functionally distinct muscle fiber-types arise is important for unraveling the molecular basis of diseases from cardiomyopathies to muscular dystrophies. In this review, we focus on recent advances in *Drosophila* and mammals in understanding how muscle fiber-type specification is controlled by the regulation of transcription and alternative splicing. We illustrate the cooperation of general myogenic transcription factors with muscle fiber-type specific transcriptional regulators as a basic principle for fiber-type specification, which is conserved from flies to mammals. We also examine how regulated alternative splicing of sarcomeric proteins in both flies and mammals can directly instruct the physiological and biophysical differences between fiber-types. Thus, research in *Drosophila* can provide important mechanistic insight into muscle fiber specification, which is relevant to homologous processes in mammals and to the pathology of muscle diseases.

Contents

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Introduction

Animals from jellyfish to humans use contractile muscle cells to perform coordinated movements. Higher animals possess distinct muscle classes that are specialised for certain tasks: the vertebrate heart pumps blood life-long without rest, smooth muscles ensheathing the gut propel food without voluntary control, and body muscles move in a precise, consciously controlled manner to enable body movements, body posturing and facial expressions. To optimally fulfill these different tasks, each muscle class requires distinct contractile, metabolic and electrophysiological properties.

The molecular basis for these functional distinctions is generated during development and results in a dramatically different morphology for each of the three muscle classes. Smooth muscles are mononucleated and can be activated by a variety of neuronal, hormonal, autocrine/paracrine signals or changes in load and length. Their contractile elements lack a regularly striated structure [30,75]. Cardiomyocytes are also mononucleated. They are activated through electrical coupling after neuronal firing and show regular striations along their myofibrils [30]. Skeletal muscle is built of many large, syncytial muscle fibers. Each muscle fiber contains many, often hundreds, of nuclei and has a defined neuromuscular junction that triggers contractions. Each fiber houses many highly ordered myofibrils that are laterally aligned to form stereotypical cross-striations [30].

In this review, we discuss recent progress on mechanisms of differential transcription and alternative splicing that instruct functional differences between muscle types. We focus on mammalian skeletal muscle and *Drosophila* body muscle as the best understood model systems. Mammalian skeletal muscle fibers are historically classified as slow (type 1, red muscle) or fast (type 2, white muscle) fibers. Fast fibers are further subdivided into type 2A, 2B and 2X. They generally can produce higher forces than slow fibers, are glycolytic and fatigue rather quickly. In contrast, slow fibers produce lower forces, primarily use oxidative metabolism and are more fatigue-resistant (reviewed in [63]). Each individual human skeletal muscle consists of many, often several hundred, muscle fibers with a characteristic fiber-type composition. For example, the extensor digitorum longus (EDL) muscle in the foot is mainly composed of fast fibers, whereas the soleus muscle in the lower leg contains mainly slow fibers. However, the individual fiber composition of each muscle will adapt to exercise regime, such that the soleus muscle of a sprint athlete will incorporate more fast fibers as compared to that of a marathon runner, which will be “slower” [12].

Patterning of mammalian muscle fiber-types

The different functional properties of skeletal muscle fiber types in mice arise during fetal muscle development and are further modified during postnatal life. The general myogenic transcription factors MyoD, Myf5, Mrf4 and Myogenin are required for the correct development of most, if not all, skeletal muscles early in embryogenesis (reviewed in [5,7]). Subdivision into distinct muscle fiber types arises during late fetal development in mice through initiation of the fetal myogenic program. It was recently shown that the expression of nuclear factor one X (Nfix) switches the embryonic to the fetal program by repressing embryonic and activating fetal myogenic genes such as muscle creatine kinase (MCK) or β-enolase [49]. This enables the next steps of fiber-type specification by the differential expression of additional transcription factors. The best studied factors are Six1 and Six4, which promote the fast fiber fate, together with their cofactor Eya1 ([25,53]). Their action is supported by the transcriptional repressor Sox6, which represses slow genes in fast fibers [28,31]. Together, this complex interplay between general and specific transcription factors establishes the typical fiber-type distribution at the end of murine fetal muscle development.

Postnatally, muscle fiber-type distribution is significantly reorganized, coinciding with substantial muscle growth after birth. Neuronal innervation, together with calcium-calcineurin signaling, is a key player at this stage. Increased calcineurin signaling promotes the slow fiber fate [67], potentially through the downstream cooperation of Mef2d with the transcriptional coactivator PGC-1α, which induces the expression of slow fiber genes, such as myoglobin, or genes required for mitochondrial oxidative metabolism [42]. Varying levels of neuronal activity, and thus calcineurin signaling, also promote the differential recruitment of NFAT family members to the promoters of activity-dependent genes. An NFATc2/3/4 complex specifies transcription of fast fiber genes, while the nuclear import of NFATc1 driven by slow nerve activity redirects the complex to activate transcription of slow genes [10]. As in embryogenesis, general muscle transcription factors cooperate with fiber type-specific transcription factors to achieve differential expression of fiber type-specific genes during adult muscle differentiation.

Fiber-type specific effectors

How do muscle fibers achieve their specific contractile properties? The best-studied examples of differentially expressed sarcomeric components in mammalian body muscle are the myosin heavy chain (MyHC) isoforms. Different fiber types express different MyHC isoforms from the various muscle myosin II genes in mammals. During the embryonic to fetal myogenic switch, embryonic MyHC is gradually replaced by neonatal MyHC. After birth, neonatal MyHC is lost and type 2A fast fibers express MyHC-2A, while slow fibers express MyHC-beta/slow (reviewed in [63]). MyHC expression is at least partially regulated by NFAT family members downstream of neuronal activity, as MyHC-slow is cooperatively controlled by all four NFAT family members, while MyHC-2A is controlled by NFATc2/3/4 [10].

While further details of upstream regulation are unclear, the expression of MyHC isoforms with different molecular properties, for example variable cross-bridge lengths with actin during contraction, underlies part of the functional differences