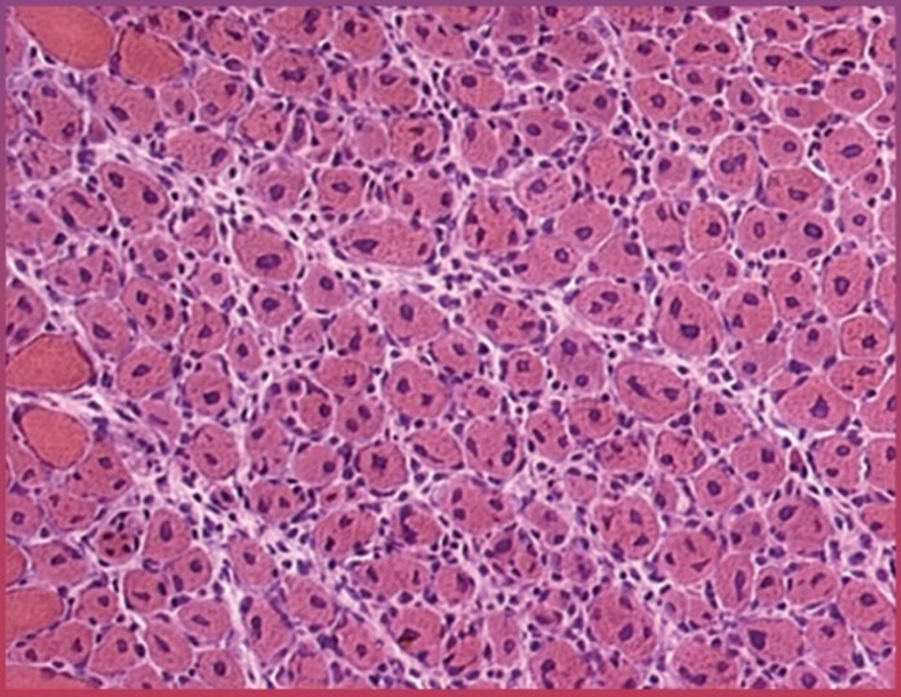
Myogenesis



Edited by

Grace K. Pavlath

VOLUME NINETY SIX

Current Topics in DEVELOPMENTAL BIOLOGY

Myogenesis

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Preface

Skeletal muscle is a vital tissue for movement, breathing, and metabolism. In addition, it is one of the few tissues that exhibit extensive regenerative ability in the adult due to the presence of stem cells called satellite cells. Skeletal muscle biology has engendered interest from numerous angles: sports medicine, developmental biology, gene regulation, physiology, immunology, and stem cells. In recent years, skeletal muscle research has rapidly expanded in many exciting directions. The goal of this book is to cover some key areas of muscle biology related to satellite and other progenitor cells, muscle regeneration, signal transduction, gene expression, and disease.

Key questions related to developmental origins of muscle and cancer (Chapters 1 and 2) as well as gene regulation and signal transduction (Chapters 3 and 4) are explored. Further areas that are discussed include the effects of nonmyogenic cells on satellite cells and muscle regeneration (Chapters 5 and 6) and how fibrosis develops when muscle regeneration is impaired (Chapter 7). Complementing these discussions on muscle regeneration is a consideration of how myoblast fusion is regulated by a recently described family of molecules (Chapter 8). New emerging areas of research include the effects of circadian rhythms on skeletal muscle function (Chapter 9) and the challenges of controlling nucleocytoplasmic transport in multinucleated myofibers (Chapter 10).

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CHAPTER ONE

Origin of Vertebrate Limb Muscle: The Role of Progenitor and Myoblast Populations

Malea Murphy *and* Gabrielle Kardon

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Abstract

Muscle development, growth, and regeneration take place throughout vertebrate life. In amniotes, myogenesis takes place in four successive, temporally distinct, although overlapping phases. Understanding how embryonic, fetal, neonatal, and adult muscle are formed from muscle progenitors and committed myoblasts is an area of active research. In this review we examine recent expression, genetic loss-of-function, and genetic lineage studies that have been conducted in the mouse, with a particular focus on limb myogenesis. We synthesize these studies to present a current model of how embryonic, fetal, neonatal, and adult muscle are formed in the limb.

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1. Introduction

Muscle development, growth, and regeneration take place throughout vertebrate life. In amniotes, myogenesis takes place in successive, temporally distinct, although overlapping phases. Muscle produced during each of these phases is morphologically and functionally different, fulfilling different needs of the animal (reviewed in Biressi *et al.*, 2007a; Stockdale, 1992). Of intense interest is understanding how these different phases of muscle arise. Because differentiated muscle is postmitotic, muscle is generated from myogenic progenitors and committed myoblasts, which proliferate and differentiate to form muscle. Therefore, research has focused on identifying myogenic progenitors and myoblasts and their developmental origin, defining the relationship between different progenitor populations and myoblasts, and determining how these progenitors and myoblasts give rise to different phases of muscle. In this review, we will give an overview of recent expression, genetic loss-of-function, and genetic lineage studies that have been conducted in mouse, with particular focus on limb myogenesis, and synthesize these studies to present a current model of how different populations of progenitors and myoblasts give rise to muscle throughout vertebrate life.

2. Myogenesis Overview

In vertebrates, all axial and limb skeletal muscle derives from progenitors originating in the somites (Emerson and Hauschka, 2004). These progenitors arise from the dorsal portion of the somite, the dermomyotome. The limb muscle originates from limb-level somites, and cells delaminate from the ventrolateral lip of the dermomyotome and migrate into the limb, by embryonic day (E) 10.5 (in forelimb, slightly later in hindlimb). Once in the limb, these cells proliferate and give rise to two types of cells: muscle or endothelial (Hutcheson *et al.*, 2009; Kardon *et al.*, 2002). Thus, the fate of these progenitors only becomes decided once they are in the limb. Those cells destined for a muscle fate then undergo the process of myogenesis. During myogenesis, the progenitors become specified and determined as myoblasts, which in turn differentiate into postmitotic mononuclear myocytes, and these myocytes fuse to one another to form multinucleated myofibers (Emerson and Hauschka, 2004).

Myogenic progenitors, myoblasts, myocytes, and myofibers critically express either Pax or myogenic regulatory factor (MRF) transcription factors. A multitude of studies have shown that progenitors in the somites and in the limb express the paired domain transcription factors Pax3 and Pax7 (reviewed in Buckingham, 2007). Subsequently, determined

myoblasts, myocytes, and myofibers in the somite and in the limb express members of the MRF family of bHLH transcription factors. The MRFs consist of four proteins: Myf5, MyoD, Mrf4 (Myf6), and Myogenin. These factors were originally identified by their *in vitro* ability to convert 10T1/2 fibroblasts to a myogenic fate (Weintraub *et al.*, 1991). Myf5, MyoD, and Mrf4 are expressed in myoblasts (Biressi *et al.*, 2007b; Kassar-Duchossoy *et al.*, 2005; Ontell *et al.*, 1993a,b; Ott *et al.*, 1991; Sassoon *et al.*, 1989), while Myogenin is expressed in myocytes (Ontell *et al.*, 1993a,b; Sassoon *et al.*, 1989). In addition, MyoD, Mrf4, and Myogenin are all expressed in the myonuclei of differentiated myofibers (Bober *et al.*, 1991; Hinterberger *et al.*, 1991; Ontell *et al.*, 1993a,b; Sassoon *et al.*, 1989; Voytik *et al.*, 1993). Identification of these molecular markers of the different stages of myogenic cells has been essential for reconstructing how myogenesis occurs.

In amniotes, there are four successive phases of myogenesis (Biressi *et al.*, 2007a; Stockdale, 1992). In the limb, embryonic myogenesis occurs between E10.5 and E12.5 in mouse and establishes the basic muscle pattern. Fetal (E14.5–P0; P, postnatal day) and neonatal (P0–P21) myogenesis are critical for muscle growth and maturation. Adult myogenesis (after P21) is necessary for postnatal growth and repair of damaged muscle. Each one of these phases involves proliferation of progenitors, determination and commitment of progenitors to myoblasts, differentiation of myocytes, and fusion of myocytes into multinucleate myofibers. The progenitors in embryonic and fetal muscle are mononuclear cells lying interstitial to the myofibers. After birth, the neonatal and adult progenitors adopt a unique anatomical position and lie in between the plasmalemma and basement membrane of the adult myofibers and thus are termed satellite cells (Mauro, 1961). During embryonic myogenesis, embryonic myoblasts differentiate into primary fibers, while during fetal myogenesis fetal myoblasts both fuse to primary fibers and fuse to one another to make secondary myofibers. During fetal and neonatal myogenesis, myofiber growth occurs by a rapid increase in myonuclear number, while in the adult myofiber hypertrophy can occur in the absence of myonuclear addition (White *et al.*, 2010).

Embryonic, fetal, and adult myoblasts and myofibers are distinctive. The different myoblast populations were initially identified based on their *in vitro* characteristics. Embryonic, fetal, and adult myoblasts differ in culture in their appearance, media requirements, response to extrinsic signaling molecules, drug sensitivity, and morphology of myofibers they generate (summarized in Table 1.1; Biressi *et al.*, 2007a; Stockdale, 1992). Recent microarray studies also demonstrate that embryonic and fetal myoblasts differ substantially in their expression of transcription factors, cell surface receptors, and extracellular matrix proteins (Biressi *et al.*, 2007b). It presently is unclear whether neonatal myoblasts differ substantially from fetal myoblasts. Differentiated primary, secondary, and adult myofibers also differ, primarily in their expression of muscle contractile proteins, including

Table 1.1 Summary of characteristics of embryonic, fetal, and adult myoblasts and myofibers

	Culture appearance and clonogenicity	Signaling molecule response	Drug sensitivity	Myofiber morphology in culture
Embryonic myoblasts	Elongated, prone to differentiate and form small colonies, do not spontaneously contract in culture	Differentiation insensitive to TGFβ-1 or BMP4	Differentiation insensitive to phorbol esters (TPA), sensitive to merocynine 540	Mononucleated myofibers or myofibers with few nuclei
Fetal myoblasts	Triangular, proliferate (to limited extent) in response to growth factors, spontaneously contract in culture	Differentiation blocked by TGFβ-1 and BMP4	Differentiation sensitive to phorbol esters (TPA)	Large, multinucleated myofibers
Satellite cells/ Adult myoblasts	Round, clonogenic, but undergo senescence after a limited number of passages, spontaneously contract in culture	Differentiation blocked by TGFβ-1 and BMP4	Differentiation sensitive to phorbol esters (TPA)	Large, multinucleated myofibers

All from Biressi *et al.* (2007b) or review of Biressi *et al.* (2007a).

	MyHCemb	MyHCperi	MyHCI	MyHCIIa	MyHCIIx	MyHCIIb
Embryonic myofibers	+	−	+	−	−	−
Fetal myofibers	+	+	+/−	+/−	+/−	+/−
Adult myofibers	−	−	−	+	+	+

Derived from Agbulut *et al.* (2003), Gunning and Hardeman (1991), Lu *et al.* (1999), Rubinstein and Kelly (2004), and Schiaffino and Reggiani (1996).