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Review

Cellular heterogeneity during vertebrate skeletal muscle development

Stefano Biressi [a,*], Mario Molinaro [b], Giulio Cossu [a,c,d]

[a] Stem Cell Research Institute, DiBiT, San Raffaele Scientific Institute, 58 via Olgettina, 20132 Milan, Italy
[b] Department of Histology and Medical Embryology, University of Rome La Sapienza, 14 Via Scarpa, 00161 Rome, Italy
[c] Department of Biology, University of Milan, 26 via Celoria, 20130 Milan, Italy
[d] Institute of Cell Biology and Tissue Engineering, San Raffaele Biomedical Science Park, 100/2 via Castel Romano, 00128 Rome, Italy

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Abstract

Although skeletal muscles appear superficially alike at different anatomical locations, in reality there is considerably more diversity than previously anticipated. Heterogeneity is not only restricted to completely developed fibers, but is clearly apparent during development at the molecular, cellular and anatomical level. Multiple waves of muscle precursors with different features appear before birth and contribute to muscular diversification. Recent cell lineage and gene expression studies have expanded our knowledge on how skeletal muscle is formed and how its heterogeneity is generated. This review will present a comprehensive view of relevant findings in this field.

Keywords: Skeletal muscle; Development; Fiber diversity; Myogenic lineage

Introduction

Skeletal muscle is the most abundant tissue in the vertebrate body. Animals have evolved individual muscle specialized to perform different types of movements. Each muscle is comprised of a variable number of contracting fibers, formed by the fusion of a large number of myogenic progenitors and thus containing up to many thousands of nuclei. Fibers are highly heterogeneous because of different anatomical, physiological and biochemical features. Most of vertebrate muscles are composed of variable proportions of different (fast or slow) fiber types determining the appropriate force and duration of contraction. During the last three decades it has become clear that this heterogeneity is not restricted to the postnatal life but also occurs during embryonic development. Distinct classes of myogenic progenitors appear to be involved in muscular patterning and growth. This review will focus on the events that determine the spatio-temporal heterogeneity of developing skeletal muscle in vertebrates: it follows and updates a previous review on the same topic (Cossu and Molinaro, 1987). Although we have tried to be as complete as possible, the wide topic covered and space limitations prevent a full discussion of all the original reports on which current knowledge in this field is based. Therefore readers will also be referred to recent reviews in specific areas.

Cellular heterogeneity in skeletal muscle development

Phenotypic and molecular diversity among skeletal muscle progenitors

It is widely accepted that all the skeletal muscles in vertebrate body, with the exception of some craniofacial muscles, derive from progenitors present in the somites (Christ and Ordahl, 1995). Somites are transient mesodermal units, which form in a cranio-caudal succession by segmentation of the paraxial mesoderm on both sides of the neural tube. Each newly formed somite rapidly differentiates into a ventral sclerotome and a dorsal dermomyotome from which myogenic precursors originate. Shortly after the onset of somitogenesis (at embryonic day E8.75 in the mouse) some myogenic precursors cells give

* Corresponding author. Present address: Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305-5235, USA. Fax: +1 650 8490436.
E-mail address: sbiressi@stanford.edu (S. Biressi).

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rise to terminally differentiated, mononucleated muscle cells (myocytes) of the primary myotome. Primary myotome formation is a multistep process in which precursors translocate from the dermomyotome to a ventrally located domain where they elongate along the axis of the embryo to span the entire somite length. This process has been intensively studied, especially in the avian embryo, but some aspects remain controversial (Cinnamon et al., 1999, 2001; Denetclaw and Ordahl, 2000; Denetclaw et al., 1997, 2001; Gros et al., 2004; Kahane et al., 1998, 2001, 2002; Kahane and Kalcheim, 1998; Ordahl et al., 2001; Venters and Ordahl, 2002). Nevertheless the final pattern is relatively simple, with all muscle cells aligned along the whole cranio-caudal length of the somite. The role of the myotome during development of higher vertebrates remains unclear. However in *Myf5*$^{nlacZ/nlacZ}$ mice, in which the expression of both *Myf5* and *MRF4* is abolished and that fail to form a primary myotome, myogenesis proceeds in a relatively normal sequence (Tajbakhsh et al., 1996) suggesting that formation of the primary myotome is not essential for later muscle development in amniotes or that, alternatively, the later development of a MyoD dependent similar structure is sufficient to drive an almost normal muscle development.

Only a fraction of myogenic progenitors terminally differentiate during primary myotome formation. As schematized in Fig. 1, skeletal muscle is established in successive distinct, though overlapping steps involving different type of myoblasts (embryonic, fetal myoblasts and satellite cells). The continued growth of muscles that occurs during late embryonic (E10.5–12.5), fetal (E14.5–17.5) and postnatal life was recently attributed to a population of muscle progenitors already present at embryonic stage (Gros et al., 2005; Kassar-Duchossoy et al., 2005; Relaix et al., 2005; Schienda et al., 2006). These skeletal muscle progenitor cells arise in the central part of the dermomyotome, co-express Pax3 and Pax7 and can differentiate into skeletal muscle fibers during embryogenesis or possibly remain as a reserve cell population within the growing muscle mass during peri- and postnatal stages. In *Pax3/Pax7* double knockout mice generation of the primary myotome is unaffected, whereas successive phases of myogenesis are compromised due to the non-myogenic fate adopted by these progenitors. It has therefore been proposed that all of the cells of the myogenic lineage (with the exception of myotomal cells) may be derived from a Pax3/Pax7 positive population of myogenic progenitors resident in the central part of the dermomyotome.

At around E11 in the mouse, embryonic myoblasts invade the myotome and fuse into myotubes, probably incorporating the initially mononucleated myocytes of the early myotome, although this has not been formally demonstrated. Grossly at the same stage, during a phase which is usually referred as primary myogenesis, myogenic progenitors, which have migrated from the dermomyotome to the limb, start to differentiate into multinucleated muscle fibers, known as primary fibers. This embryonic phase appears to depend upon MRF4 since it is maintained in the Myf5 null embryo but is disrupted in the Myf5-MRF4 double mutant embryo (Kassar-Duchossoy et al., 2004). A new wave of myogenesis takes place between E14.5 and E17.5. This phase is called secondary myogenesis and involves fusion of fetal myoblasts either with each other to give rise to secondary fibers (originally smaller and surrounding primary fibers) (Duxson et al., 1989) and also with primary fibers (Dunglison et al., 1999; Evans et al., 1994). It is only at the end of this phase that satellite cells can be morphologically identified as mononucleated cells lying between the basal lamina and the fiber plasma membrane. During peri- and postnatal development, satellite cells divide at a slow rate and a large part of the progeny fuse with the adjacent fiber to contribute new nuclei to growing muscle fibers (whose nuclei cannot divide), so that the majority of the nuclei of a mature muscle are presumably derived from

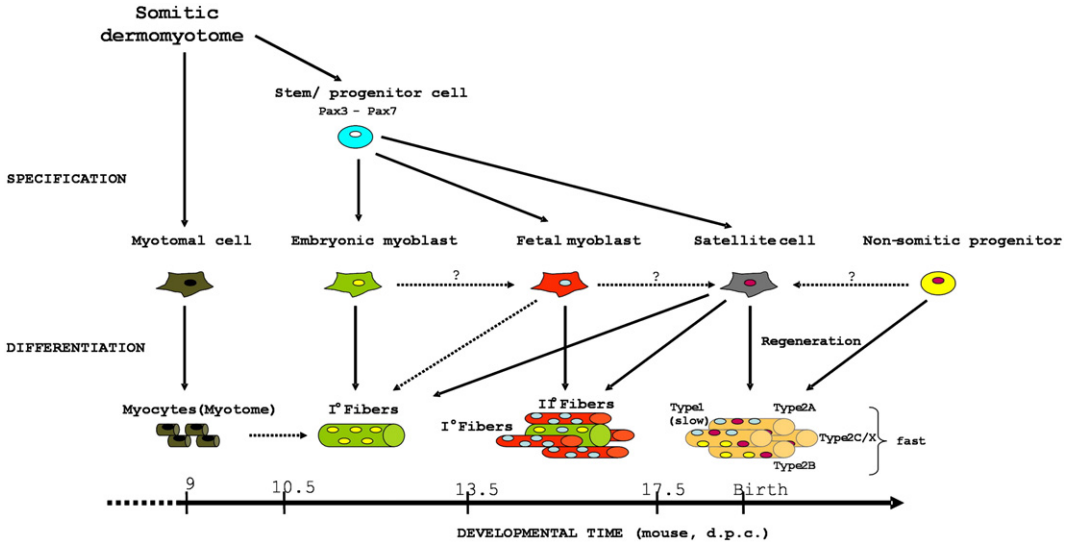

Fig. 1. Proposed lineage scheme for skeletal muscle. The somitic dermomyotome is the origin of the myotomal cells, which differentiate into the myocytes of the early myotome. Pax3/Pax7 positive cells identified in the dermomyotome release muscle precursors during development (embryonic, fetal myoblasts and satellite cells). Embryonic and fetal myoblasts give rise to 1° and 2° fibers, respectively. Satellite cells appear at the end of gestation and are responsible for postnatal growth and regeneration. Other non-somitic progenitors are involved in muscle regeneration, although their role in non-pathological conditions remains largely unexplored. Abbreviations used: d.p.c. days *post coitum*. An indicative timing of murine development is depicted.

satellite cells. At the end of postnatal growth, satellite cells enter a phase of quiescence but can be activated if the muscle tissue is damaged or in response to further growth demands. In these cases satellite cells undergo a number of cells divisions producing fusion competent cells that can either fuse with damaged fibers or form new ones, and other cells that return to quiescence, thus maintaining the progenitor pool. This fact has led to the suggestion that they represent a type of stem cells (Collins et al., 2005). It has also been recently shown that other cell types, which are not somitic in origin, such as hematopoietic and different types of mesodermal stem cells, have the potential to participate to muscle regeneration, though their contribution appears to be minimal under normal circumstance (reviewed in Cossu and Biressi, 2005).

Previous work from different laboratories identified specific features of embryonic, fetal myoblasts and satellite cells that characterize them as distinct classes of myogenic cells (Cossu and Biressi, 2005; Cossu and Molinaro, 1987; Miller et al., 1999; Stockdale, 1992). When explanted in culture these different types of cells differ dramatically in their behavior. Embryonic myoblasts are elongated cells (Fig. 2A) that differentiate into mononucleated or oligonucleated myotubes. Their differentiation is not inhibited by molecules such as TGFβ, BMP-4 or phorbol esters. Embryonic myoblasts are more prone to differentiation and in keeping with this they generate smaller colonies than their late-appearing counterparts when cultured at clonal dilution *in vitro* (Biressi et al., 2007). Moreover embryonic myoblasts present a different sensitivity to merocynine 540 (Nameroff and Rhodes, 1989). Fetal myoblasts show in the mouse a triangular shape (Fig. 2B) and proliferate to a limited extent in response to growth factors, differentiate into large multinucleated myotubes and this differentiation is inhibited by TGFβ, BMP-4 and phorbol esters. Satellite cells are the only real clonogenic cell in the myogenic lineage of the mouse, although they undergo senescence after a limited number of passages *in vitro*. They show a round shape morphology (Fig. 2C) and also form large myotubes whose differentiation is sensitive to TGFβ and BMP, but not to phorbol esters. Moreover satellite cells present a high PDGF binding capacity (Yablonka-Reuveni and Seifert, 1993), early expression of acetylcholine receptors and acetyl-cholinesterase, differential ability to respond to topographical guidance cues (Evans et al., 1999) and peculiar expression of several muscle specific genes (Hartley et al., 1991). Recently, a whole genome wide expression analysis was carried on by micro-array analysis and real-time PCR on purified embryonic and fetal myoblasts (Biressi et al., 2007). This gene expression analysis identified many differentially expressed genes, clearly revealing that embryonic and fetal myoblasts are intrinsically different populations of myoblasts which possess distinct genetic programs. Interestingly, the profile of gene expression of the myogenic cell line C2C12, originally established from adult regenerating muscle and thus considered a model of satellite cells, showed many similarities with that of fetal myoblasts, suggesting that satellite cells and fetal myoblasts could be more related to each other.

Asynchronous differentiation during muscle development

Embryonic myogenesis begins in newly formed somites where dorsally located progenitors respond to signals such as Wnts and Shh emanating from adjacent neural tube, notochord and ectoderm, and activate the basic helix–loop–helix transcription factors *Myf5* and *MyoD* that commit cells to myogenesis (Cossu et al., 2000; Pownall et al., 2002 and references therein). Embryonic myogenesis occurs in somites and later in the limbs, in the absence of already formed muscle fibers. In the case of the somite, myotomal cells differentiate into myocytes of the primary myotome, which represents the first terminally differentiated muscle in the embryo. Embryonic myogenesis in the limb also occurs in the absence of pre-existing muscle fibers, whereas fetal myogenesis, postnatal muscle growth and muscle regeneration occur within a pre-existing micro-environment of growing, damaged or regenerating muscle fibers. Within such an environment, myogenic progenitors can either fuse with a pre-existing fiber or with similar cells to form a new myotube that will eventually mature into a new fiber. For example, during fetal myogenesis, fetal myoblasts mainly fuse with each other, giving rise to secondary (fetal) fibers that surround primary fibers, although a minority fuse with existing primary fibers (Evans et al., 1994). Signals dictating these processes are still largely unknown although it has been proposed that VLA-4/VCAM-1 interactions may influence the alignment of secondary myoblasts along primary myotubes and/or the fusion of secondary myoblasts (Rosen et al., 1992).

However, the observation that only a proportion of myogenic progenitors present in the dermomyotome terminally differentiate during somitogenesis and that other myogenic cells differentiate in successive phases suggests that cells situated in the

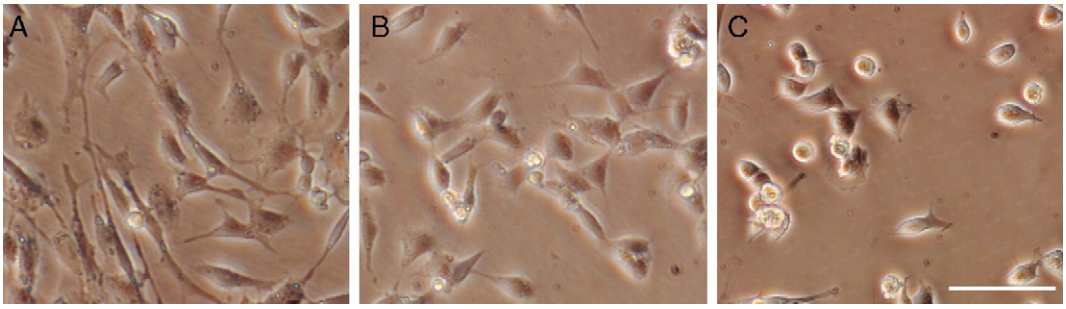

Fig. 2. Different morphology of myogenic cells. Murine embryonic (A), fetal (B) myoblast and satellite cells (adult myoblasts) (C) were cultured in 20% fetal calf serum containing medium. Phase contrast. Scale bar, 50 μm. Note the presence of elongated cells in the embryonic culture.

same environment may respond differently to the same signals. This different fate could thus depend upon intrinsic properties of the cells. The Pax3/Pax7^{+} muscle progenitor cells may therefore represent a mixed population of cells with differing developmental potential. Supposing that all canonical myogenic cells (embryonic and fetal myoblasts and satellite cells) are specified to myogenesis in the newly formed somite, a proportion of these cells must be kept in a committed but undifferentiated state until subsequent phases of myogenesis. In *Drosophila*, lateral inhibition through *Notch/Delta* signaling has been identified as the probable mechanism by which adult myogenic progenitors are selected in response to *Wng* signaling (Baylies et al., 1998). Recently a similar mechanism has been shown to operate in adult muscle (Conboy and Rando, 2002) and it is possible that this may play a role in the mammalian somite. Indeed, several Delta and Notch isoforms are expressed in somites and Notch signaling has been shown to inhibit myogenesis (Nofziger et al., 1999; Wilson-Rawls et al., 1999). Nevertheless, although an asymmetric expression of the Notch antagonist, Numb, was documented in the central part of the dermomyotome (Holowacz et al., 2006) and premature differentiation and depletion of Pax3+/Pax7+ progenitors was observed in hypomorphic Delta-1 embryos (Schuster-Gossler et al., 2007), direct evidence for a role of Notch in diversifying cell fate in mammalian somites is still lacking. Interestingly, a crosstalk between Notch and BMP or TGFβ signaling pathways has been recently documented by different reports and an activated Notch pathway appears to be necessary for TGFβ and BMP-4-mediated inhibition of differentiation in both satellite cells (Blokzijl et al., 2003; Dahlqvist et al., 2003) and fetal myoblasts (Biressi et al., 2007). One possible mechanism to enable certain myoblasts/progenitors to differentiate in an environment that is permissive for proliferation for others may be based on the inability of these cells to respond to growth factors and/or to molecules, which inhibit differentiation. Interestingly embryonic myoblasts are insensitive to TGFβ and BMP-mediated inhibition of differentiation and fetal myoblasts have a low binding capacity to PDGF, which conversely efficiently promotes proliferation and thus represses differentiation of satellite cell (Yablonka-Reuveni and Seifert, 1993). These observations sustain a model (Fig. 3) in which TGFβ and/or BMP might influence the process of primary fibers formation, by inhibiting differentiation of fetal myoblasts and satellite cells but not of embryonic myoblasts (Cusella-DeAngelis et al., 1994). In this way, non-dividing embryonic myoblasts can undergo differentiation, forming primary fibers. Once formed, primary fibers may stimulate (possibly trough secretion of mitogens such as FGFs) a new wave of proliferation in fetal myoblasts in order to expand the pool of cells needed to form secondary fibers. At the fetal stage, the levels of expression of TGFβ and/or BMP should decrease or their action should be counteracted by still unknown mechanisms and fetal myoblast differentiation and fusion may occur. Nevertheless, since satellite cells do not undergo differentiation at this time, the control of proliferation and differentiation in these cells may also be different. Thanks to its different action on fetal myoblasts and satellite cells, PDGF may be involved in the transition from fetal to adult myogenesis and contribute to maintain a population of undifferentiated cells in the postnatal and in the adult muscle.

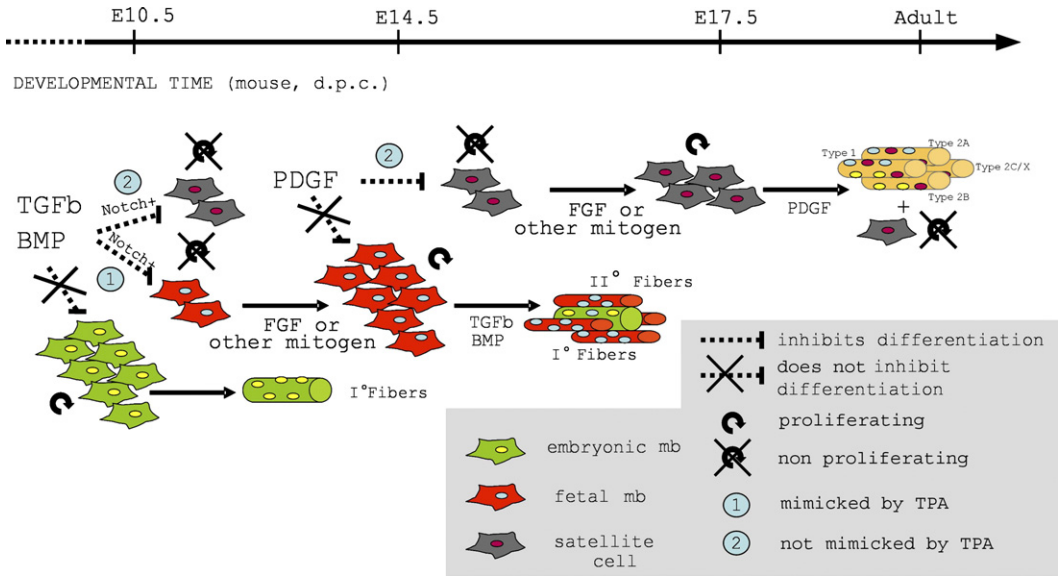

Fig. 3. A possible model for the regulation of muscle fiber formation. During primary myogenesis embryonic myoblasts fuse into primary fibers, whereas fetal myoblasts and satellite cells are maintained in an undifferentiated state by TGFβs and BMPs. The action of TGFβs and BMPs can be mimicked by TPA only in the case of fetal myoblasts, whereas their action on both satellite cells and fetal myoblasts depends on the activation of the Notch pathway. Once formed primary fibers may release mitogens which induce in fetal myoblasts a new wave of proliferation. At fetal stage, the levels of TGFβs and BMPs should decrease allowing fetal myoblasts to differentiate and form secondary fibers. At this stage, PDGF may maintain satellite cells in an undifferentiated state. Subsequently, local changes in the exposure of satellite cells to PDGF and to other still undefined factors may regulate their proliferation and differentiation, thus regulating their fusion to previously formed fibers during postnatal development and their maintenance in a quiescent state in adult uninjured muscles. An indicative timing of murine development is depicted. Arrows indicate progression toward proliferation and then differentiation. The size of the font reflects the concentration of the growth factors at different developmental time. Abbreviations used: d.p.c. days *post coitum*.

While the proposed model is probably an oversimplification of the real situation and the molecular mechanisms operating in these cells still remain largely unexplained, it is clear that the different phases of myogenesis need to be finely regulated to achieve a correct muscle formation.

Fiber diversity in skeletal muscle

Primary and secondary fibers

All muscle fibers are produced by the fusion of myogenic cells. However, fiber formation in vertebrates is multiphasic occurring in early and late waves (Kelly and Zacks, 1969). During the early phase (primary myogenesis), primary fibers are generated by the fusion of embryonic myoblasts. During primary myogenesis muscles consist of small numbers of myotubes that progressively increase in size and get a characteristic round shape in transverse section. During the later wave (secondary myogenesis), secondary fibers are generated by the fusion of fetal myoblasts. Secondary fibers form initially at site of innervation of the primary fiber and are surrounded by the same basal lamina as the primary fiber on which they lie (Duxson et al., 1989). The secondary myotubes remain attached for a short period to primary fibers and subsequently elongate and become independent fibers, which can be distinguished from primary fibers by their relative small size (Kelly and Zacks, 1969). The innervation of muscles starts while fibers are still forming. Each muscle fiber is initially innervated by multiple axons, all but one of which are subsequently eliminated. Postnatally, all the muscle fibers that remain contacted by the axon branches of an individual motor neuron are of the same type. The mechanisms whereby nerves become associated with fast or slow muscle fibers are currently unknown, but it has been generally assumed that nerve plays a role in generating fiber type diversity. In the absence of functional innervation the formation of muscle fibers is impaired, leading to a reduction in the total number of fibers, with primary fibers being in general less affected than secondary. Chronic denervation leads to eventual degeneration of both primary and secondary fibers (reviewed in McLennan, 1994; Wigmore and Evans, 2002).

Primary and secondary fibers differ in the expression of myosin heavy chain (MyHC) isoforms. In mammals, primary fibers express embryonic (fast) and I/β(slow)-MyHC and shortly before the end of primary fiber formation, some (generally located on the superficial edge of the muscles) also express the perinatal/neonatal (fast) isoform. In contrast, secondary fibers express the fast embryonic and perinatal isoforms from their inception and (with the exception of the soleus muscle) do not express I/β(slow)-MyHC. Thus, in general, mammalian primary fibers (and embryonic myotubes *in vitro*) are programmed for a predominantly slow phenotype, whereas secondary fibers (and fetal myotubes *in vitro*) adopt a fast phenotype (reviewed in Wigmore and Evans, 2002; Zhang et al., 1998). In addition to MyCH isoforms, several other genes, such as *muscle creatine kinase*, *β-Enolase* and *PkCθ* have been reported to be differentially expressed in primary and secondary fibers (Barbieri et al., 1990; Ferrari et al., 1997; Zappelli et al., 1996).

In *Myogenin*$^{-/-}$ mice secondary myogenesis appears to be mainly affected (Venuti et al., 1995). Similarly, in *Myf5*$^{-/-}$:*MyoD*$^{-/-}$ mice secondary myogenesis (but not primary myogenesis in trunk muscles) is completely abolished indicating that Myf5, MyoD and MRF4 can each independently initiate the myogenic program during primary myogenesis, whereas only Myf5 and MyoD can fulfil this role during secondary myogenesis (Kassar-Duchossoy et al., 2004). Also mice over-expressing *Ncam* (Fazeli et al., 1996) and *Met* mutants, in which *Grb2* mediated signaling is abrogated (Maina et al., 1996) show an altered secondary myogenesis. Conversely, replacement of *Integrin β1A* by *Integrin β1D* by a knock-in strategy leads to an impaired primary, but not secondary myogenesis (Cachaco et al., 2005). Finally, genes such as *Nfatc3* (Kegley et al., 2001) and *Trio* (O'Brien et al., 2000) which respectively affect primary and secondary myogenesis have been also identified, providing further evidence of the different nature of primary and secondary fibers in vivo.

Adult slow and fast fibers

During late pre- and postnatal development a large number of satellite cells fuse into both primary and secondary fibers. It has been estimated that more than 90% of the nuclei of a fully mature muscle are derived from adult myoblasts, likely originating predominantly from satellite cells (Zhang et al., 1998). Once muscle development is complete, primary and secondary fibers cannot be distinguished morphologically. However, adult muscle fibers are highly heterogeneous. The classification of adult muscle fibers is based on their speed of contraction, which depends mainly on the ATPase activity of the predominant myosin isoform with fast and slow fibers containing isoforms with higher and lower ATPase activity, respectively. In rodents, a single slow MyHC gene has been identified which is subject to different post-translational modifications (Maggs et al., 2000) during pre- and postnatal life. In contrast, embryonic and perinatal MyHC isoforms are progressively replaced postnatally with the three adult fast MyHCs, IIa, IIx(d) and IIb (Schiaffino and Reggiani, 1994). Adult rodent fibers can be divided into four major classes according to their speed of contraction and the predominant expression of a particular isoform of MyHC: Type I, Type IIA, Type IIX/D and Type IIB, with Type I being the slowest and Type IIB the fastest (reviewed in Wigmore and Evans, 2002; Zhang et al., 1998). Notably in humans, the *MyHC IIb* isoform is present in the genome (Weiss et al., 1999) but is not expressed (Smerdu et al., 1994). The boundaries between the different classes of adult fibers are not absolute and intermediate fibers co-expressing different MyHC isoforms are common. In addition to MyHCs, a large number of genes are also expressed at different levels in the different adult fiber types (Bottinelli and Reggiani, 2000 and references therein). Furthermore, fiber types are not fixed, but can change in response to several stimuli (Pette and Staron, 1997): for example, changes in the functional demands, electrical stimulation, cross innervation and thyroid hormone levels are able to convert fibers from one type to another (Buller et al., 1960; Hamalainen and Pette, 1996; Li et al., 1996). In general fibers convert to the

next fast or to slow forms (i.e. a fiber IIB will change into IIX/D but not to IIA or I while a fiber IIA, depending upon a slow or fast electrical stimulus, may change to type I or IIX/D respectively, but not to IIB). The presence of intermediate fibers could reflect this transition; the fact that this transition cannot be completed indicates an inherent fast/slow phenotype. The molecular mechanism which mediates the response to changes in functional demand appears at least in some cases to be mediated by the calcium-activated phosphatase calcineurin pathway (Olson and Williams, 2000; Serrano et al., 2001). Activation of the Ras pathway (Murgia et al., 2000) has also been proposed as a signaling pathway by which the changes in functional demands can modify the fiber type composition of adult muscle. Nevertheless, it is important to underline that several studies suggest that satellite cells play an important role in these adaptive responses (Martins et al., 2006; Putman et al., 1999; Putman et al., 2000). The observation that many models used to investigate fiber-type transitions could include unrecognized events such as injury, activation of satellite cells and increased nucleation of fibers (for example chronic stimulation is frequently associated with fiber damage and regeneration) challenged the hypothesis of a direct, satellite cells independent modification of the fibers induced by the environment.

The relationship between developing and mature muscle fiber phenotypes

The majority of nuclei in mature fibers are derived from satellite cells and it remains unclear whether the characteristics of an adult fiber simply reflect the numerically dominant satellite cell nuclei or if the myoblasts which first form the fiber continue to profoundly influence the proprieties of the mature fiber. There is evidence to suggest that the different properties of an adult fiber could result from heterogeneity in the satellite cell population. For example, adult myoblast derived from cat jaw muscles has a specific commitment to express jaw-specific myosins (Hoh and Hughes, 1991) and satellite cells of slow- or fast-twitch muscles show different proprieties *in vitro* (Feldman and Stockdale, 1991; Rosenblatt et al., 1996). Similarly, although myoblast lineages in the postnatal rodent seem not to be responsible for the maintenance of fiber type pattern (Hughes and Blau, 1992), Kalhovde et al. (2005) showed that "fast" and "slow" muscle fibers in hind limb muscles of adult rats regenerate from intrinsically different satellite cells. On the other side, the "slow" phenotype of mammalian primary fibers and the "fast" phenotype of secondary fibers suggest that they may give rise respectively to slow and fast contracting fibers in the adult (Kelly and Rubinstein, 1980). It should also be noted that few new nuclei are added at any given time and thus represent a minority of the total nuclei in a fiber at any developmental phase. Thus it may be possible that signals from pre-existing nuclei may reprogram newly added ones. Using real-time PCR we recently observed that highly purified (more than 98%) primary (embryonic) myotubes express slow genes while secondary (fetal) myotubes express fast genes in an in vitro environment (Biressi et al., 2007). This observation proves that murine embryonic and fetal muscle cells are intrinsically preprogrammed for a slow and fast phenotype since the observed differences were independent from nerve, hormones and even from other cells types present in vivo or in unpurified cultures. Although avian embryonic myoblasts appear also to be autonomously committed to particular fates in vivo (Nikovits et al., 2001), it is unlikely that the final fiber composition of the muscles could depend exclusively on the intrinsic genetic signature of the myogenic progenitors. Each muscle has a characteristic fiber type distribution, often with fast fibers tending to be more superficial than slow fibers. This suggests that the final pattern of fiber type, which is similar in all individuals of a given specie, may be achieved in a complex fashion, where primary and secondary fibers are patterned by signals from adjacent tissues (nerves, vessels, fibroblasts) which may release molecules, such as BMP, Shh or members of the *Wnt* gene family, which are also involved in the initiation of myogenesis in the somites (reviewed in Cossu and Borello, 1999). Motor innervation also appears to play an important instructive role in determining fiber type specification. However, myotubes from fetal slow muscle express slow MyHC only when co-cultured with neural tube, whereas muscle cells from fetal fast muscle do not express slow myosin even in the presence of neural tube, suggesting that the expression of MyHC isoforms during development is probably regulated by both myoblast lineage and innervation (DiMario and Stockdale, 1997). In conclusion the characteristics of a mature fiber are probably determined both by extrinsic factors and by intrinsic properties, although which exerts the major influence is unclear.

Intrafusal fibers

The fiber types described above are referred as extrafusal fibers. These are numerous and relatively large and are responsible for the maintenance of posture and locomotion. Mammalian muscle also contains intrafusal fibers, which are relatively rare and of small diameter. The contribution of intrafusal fibers to the generation of muscle tension is negligible but they are important for the control of muscle contraction by monitoring changes in muscle length, which are then transduced into proprioceptive signals by afferent (sensory) neurons and transmitted to the central nervous system. Mice lacking *neurotrophin 3* (Ernfors et al., 1994) or its receptor *TrkC* (Klein et al., 1994), *Egr3* (Tourtellotte and Milbrandt, 1998) or *Erbb2* (Andrechek et al., 1992) exhibit a severe defect in proprioception due to a lack of intrafusal fibers, illustrating the role of muscle spindles in the control of movements and posture. Muscle spindles consist of three types of intrafusal fibers, classified according to the organization of the nuclei: nuclear bag2, nuclear bag1 and nuclear chain fibers (reviewed in Maier, 1997; Walro and Kucera, 1999). Furthermore, each intrafusal fiber type expresses a characteristic profile of MyHC isoforms. In contrast to extrafusal fibers, developmental (i.e. embryonic and neonatal/perinatal) and slow MyHC isoforms predominate in adult intrafusal fibers (Kucera and Walro, 1990a; Kucera and Walro, 1989; Pedrosa-Domellof et al., 1991; Pedrosa et al., 1989, 1990). It has been hypothesized that intrafusal fibers may develop from precursors (embryonic and fetal myoblasts)

common to extrafusal fibers (Kucera and Walro, 1995; Kucera and Walro, 1990b) and that expression of developmental MyHC isoforms could be maintained in intrafusal fibers. In particular, these differences in MyHC profile between extrafusal and intrafusal fibers are thought to depend, at least in part, on the action of sensory innervation (Kucera and Walro, 1988).

Anatomical heterogeneity in skeletal muscle

Epaxial and hypaxial myogenesis

A complex array of muscles is present in the vertebrate body. Based on their innervation pattern it is possible to distinguish epaxial muscles, which are innervated by the dorsal branch of the spinal nerves, and hypaxial muscles, innervated by the ventral branch. Epaxial muscles are located dorsally and correspond to the deep muscles of the back in amniotes, whereas hypaxial muscles are located superficially, laterally and ventrally and include the diaphragm, body wall and limb muscles. In amniotes all of the trunk muscles are derived from the somitic dermomyotome. Myogenic progenitors derived from the dermomyotome give rise to the myotome, located between the dermomyotome and the medio-ventrally located sclerotome. In addition, some progenitors undergo a ventral migration towards sites of hypaxial myogenesis such as the limb or the tongue. Each dermomyotome and myotome can be subdivided into a more ventro-laterally located hypaxial region which gives rise to hypaxial muscles and an epaxial region located dorso-ventrally from which the epaxial muscles are formed (reviewed in Cossu et al., 2000). Work from several laboratories has shown that only the precursors of the epaxial muscles are dependent upon signals from axial structures, whereas precursors of the hypaxial muscles do not require neural tube and notochord for the myogenic commitment, but rather require signals from the dorsal ectoderm (Fig. 3). In particular, it has been shown that axial structures, probably through the release of Shh and Wnt1, preferentially activate a myogenic program by inducing Myf5 expression. In contrast, dorsal ectoderm activates the myogenic program through a MyoD-mediated pathway by releasing Wnt7a (reviewed in Cossu and Borello, 1999; Cossu et al., 2000). This is consistent with the phenotype observed in *Myf5* and *MyoD* knockout embryos since the former have early epaxial muscle defects, whereas the latter show delayed myogenesis in the limbs. In both cases the other myogenic determination genes are able to support an almost normal skeletal muscle development (Kablar et al., 1997; Rudnicki et al., 1992). Interestingly, distinct *cis*-regulatory elements controlling the expression of *Myf5* in different portions of the myotome have been identified (Hadchouel et al., 2003), and more recently, the transcription factors En1 and Sim1 have been proposed as markers respectively of the epaxial and hypaxial portion of the dermomyotome in the chick (Cheng et al., 2004b) (Fig. 4).

At the limb level, myogenic progenitors delaminate from the ventro-lateral domain of the dermomyotome (hypaxial region) and migrate distally to the limb bud where they start to express the myogenic determination genes. Once the myogenic program has been activated, the myoblasts differentiate and fuse into discrete clusters, corresponding to the major muscle masses of the dorsal and ventral aspects of the developing limb where successive phases of myogenesis (secondary and postnatal) generate the definitive limb muscles. These migrating myogenic progenitor cells express several different genes, which are essential for their function (Dietrich, 1999; Francis-West et al., 2003). Pax3 is expressed throughout the entire dermomyotome,

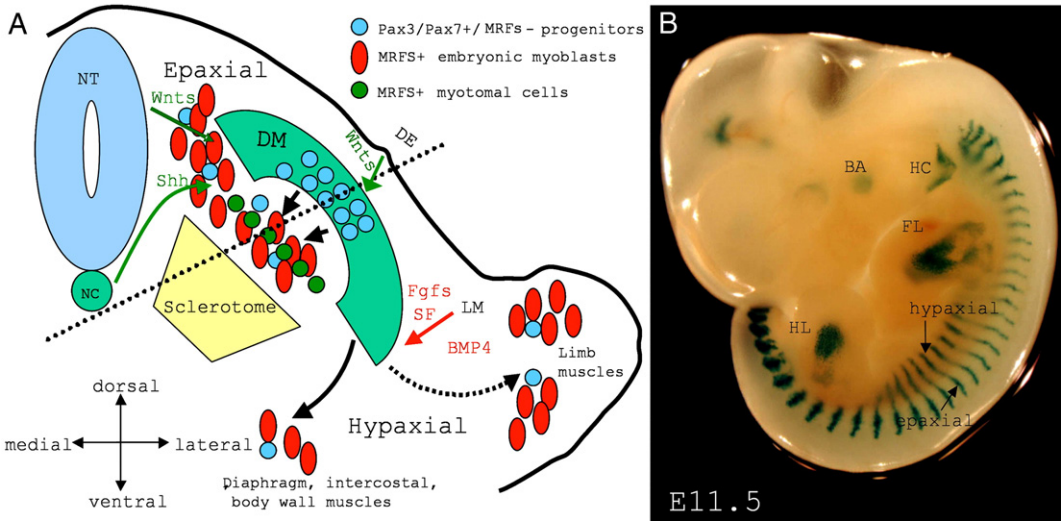

Fig. 4. Epaxial and hypaxial myogenesis. (A) Model showing the early phases of myogenesis. Myotomal cells and embryonic myoblasts, specified from a Pax3/Pax7+ population of progenitors, invade the area between the dermomyotome and the sclerotome generating the myotome. The dorso-medial domain of the myotome/dermomyotome will give rise to the epaxial (back) muscles, whereas from the ventro-lateral domain the hypaxial muscles will be generated. Surrounding tissues induce myogenesis in the epaxial and hypaxial domains with different mechanisms involving different molecules (see text). At the limb level $Pax3^{+}$, $MRFs^{-}$ progenitors migrate from the ventro-lateral (hypaxial) domain of the dermomytome to the limbs, where they activate the myogenic program. Different signaling molecules such as FGFs, BMPs and Scatter Factor (SF) are likely to regulate these events. (B) X-Gal staining of a $Myf5^{+/nlacZ}$ E11.5 embryo (Tajbakhsh et al., 1996). β-Galactosidase expression marks the areas of the embryo where the myogenic program is activated. Abbreviations used: DM dermomyotome; NT neural tube; NC notochord; DE dorsal ectoderm; LM lateral mesoderm; MRFs myogenic regulatory factors; BA branchial arches, HC hypoglossal cord; FL forelimb; HL hind limb.

but is up-regulated laterally. In the absence of *Pax3* and its downstream target *c-Met*, the limb myogenic progenitors in the lateral dermomyotome are unable to undergo normal delamination and migration (Bober et al., 1994; Dietrich et al., 1999; Goulding et al., 1994; Relaix et al., 2004). In addition, following inactivation of the *Lbx1* gene, another target of Pax3, the premyogenic cells delaminate, but appear unable to migrate (Schafer and Braun, 1999). A similar phenotype has been reported in animals in which the c-Met signaling transducer *Gab1* has been mutated (Sachs et al., 2000). *Mox2*$^{-/-}$ mice show a down-regulation of the expression of Myf5 and Pax3 and perturbed limb muscles (Mankoo et al., 1999). Interestingly, a subset of premyogenic cells migrating to the limb express the transcriptional repressor Msx1, which has been shown to block myogenic differentiation (Bendall et al., 1999). During delamination, migration and differentiation, premyogenic limb cells receive signals from the surrounding tissues (i.e. lateral plate mesoderm, apical ectoderm ridge, limb ectoderm and mesenchyme), including hepatic growth factor (HGF/SF: the ligand for c-Met) (Dietrich et al., 1999; Heymann et al., 1996), fibroblast growth factors (FGFs) (Robson and Hughes, 1996), Shh (Kruger et al., 2001) and different members of the TGFβ superfamily, such as bone morphogenic proteins (BMPs) (Pourquie et al., 1996) and myostatin (Amthor et al., 2002). Interestingly, many of these signals appear to have an important role not only in limb muscle development, but also in the regulation of the activation, proliferation and differentiation of satellite cells (Allen and Boxhorn, 1989; Allen et al., 1995) and in the control of muscular growth in general (McPherron et al., 1997).

Migratory myogenic progenitors are also found in the lateral domain of the occipital/cervical somites from where they migrate to contribute to the muscles of the tongue and larynx. The progenitors involved in this process are characterized, as are limb pre-myogenic cells, by the expression of Lbx1. In contrast hypaxial progenitors located at the interlimb level do not express Lbx1 and rather than undergoing long range migration, they enter the ventral part of the underlying myotome and progressively extend ventrally to generate the hypaxial body wall and intercostal muscles (Dietrich, 1999). Interestingly, this strategy is adopted both at the fin and interfin level in the primitive chondrichthyan sharks (Dohrn, 1884; Neyt et al., 2000), suggesting that this represents the ancestral mode of hypaxial muscle formation and that the migratory strategy observed at the limb level in amniotes appeared only successively during evolution. The observation that the teleost zebrafish uses the migratory mode similar to amniotes suggests that this strategy has been adopted before the evolution of the tetrapod limb (Neyt et al., 2000).

Head and trunk myogenesis

The craniofacial muscles are intricate muscles with less well understood mechanisms involved in their generation. Unlike muscles of the trunk and limbs, which are all somitic in origin, head muscles arise from three distinct regions of the embryo; namely the occipital somites, precordal (cranial to the notochord) and paraxial (flanking the notochord) head mesoderm. Craniofacial skeletal muscles can be subdivided in distinct classes: extraocular; branchial; somite-derived axial and hypoglossal cord-derived muscles (recently reviewed in Noden and Francis-West, 2006).

Extraocular muscles, which move and maintain the rotational stability of the eye, are derived from precordal and paraxial head mesoderm. They have metabolic and fiber type compositions distinct from most trunk muscles (Cheng et al., 2004a), with some fibers expressing unique superfast MyHC isoforms (Hoh and Hughes, 1991). The progenitors of the branchiomeric muscles originate from the paraxial head mesoderm. With the emergence of terrestrial vertebrates, the branchial arch underwent significant modification, with many muscles associated with the more caudal arches being lost. Muscles associated with the jaw (first and second branchial arches) are variable between species, reflecting evolutionary changes associated with different masticatory movements. The first five somites (occipital somites) give rise to the muscles that elevate or rotate the skull. These muscles can also be divided into epaxial and hypaxial, as with other trunk muscles. Moreover, the ventro-lateral domain of the dermomyotome of the occipital somites is the source of myogenic progenitors which aggregate ventrally on both sides of the head into the hypoglossal cord, which contributes to the tongue and laryngeal muscles (see Noden and Francis-West, 2006; Wigmore and Evans, 2002 and references therein).

Most of the progenitors of the head muscles that originate in the unsegmentated head mesoderm emigrate from their sites of origin as condensed premuscular masses of cells and not as individual myoblasts, the same strategy as adopted in the limbs. Interactions with neural crest cells appear to be important in this process. After migration, endothelial and neural crest cells invade the muscle mass and the segregation of individual muscles takes place (Noden and Francis-West, 2006). Head muscles are also established in successive phases involving the generation of secondary fibers in close association to previously formed primary fibers, although the timing of these phases is different (Wigmore and Evans, 2002).

The pattern of gene expression in head muscles is highly variable, both between each other and in comparison with trunk muscles. Several head muscles express MyHC isoforms that are not present in adult trunk muscles. Specifically, developmental isoforms such as perinatal or embryonic MyHCs are maintained in the adult. In addition, the cardiac isoform MyHCα and certain fast isoforms necessary for the rapid contraction (extraocular MyHC or superfast IIm-MyHC) are expressed in some head muscles (Hoh, 2005; Hoh and Hughes, 1991; Schachat and Briggs, 2002). There are also differences in gene expression during embryonic development. All head muscles, like those of the trunk, express members of the MyoD family during differentiation, although the initial expression of Myf5 and MyoD is delayed in comparison to most somitic muscles (Hacker and Guthrie, 1998). Indeed, embryos lacking all the three myogenic determination genes *Myf5*, *MyoD* and *MRF4* completely lack skeletal muscles in any anatomical location, including the head (Kablar et al., 1997; Kassar-Duchossoy et al., 2004). Although different regulatory sequences drive the expression of Myf5 and MyoD in different parts of the embryo (Hadchouel et al., 2003;

Kucharczuk et al., 1999; Summerbell et al., 2000; Zammit et al., 2004), no candidate upstream regulators for head muscles have been identified. Significantly, Pax3, which plays an important role in trunk muscle development (Bober et al., 1994; Goulding et al., 1994; Relaix et al., 2004, 2005; Tajbakhsh et al., 1997), is not expressed in head muscles and no muscular defects are present in the head of *Pax3* mutant mice. Head muscle myogenesis is also maintained in mice in which the expression of *Pax3*, *MRF4* and *Myf5* has been abolished (Tajbakhsh et al., 1997). Another intriguing difference is that MRF4, which can act as a muscle determination gene during embryonic myogenesis in the trunk, cannot fulfil the same role in the head (Kassar-Duchossoy et al., 2004). Some head muscles can be selectively perturbed through the action of the homeobox gene *Tbx1* (Kelly et al., 2004) or the repressors *MyoR* and *Capsulin* (Lu et al., 2002), further indicating significant differences between the head and somitic myogenic programs. In addition, the expression of other regulatory genes and the results of chick–quail transplantation experiments have also shown that distinct regulatory cascades act during head and trunk myogenesis (Borue and Noden, 2004; Mootoosamy and Dietrich, 2002).

Rostro-caudal identity

Although morphologically very similar, somites differentiate into distinct mesodermal tissues, depending on their axial level. The identity of the somite is specified by a unique expression profile of *HOX* genes, generally referred as "HOX code" (Burke, 2000). Classical transplantation experiments have shown that this segmental identity is able to influence the fate of sclerotomal (vertebrae and ribs) and non-myogenic dermomyotomal (back dermis and scapula) derivatives of the somite (Ehehalt et al., 2004; Jacob et al., 1975; Kieny et al., 1972; Mauger, 1972). In contrast, it was generally accepted for many years that somitic myogenic precursors are completely naive and do not possess positional information, depending exclusively on extrinsic cues to direct site-specific fate. This view, based on classical embryological experiments in the chick (Christ et al., 1977), in which somites were heterotopically transplanted at the limb level such that the generation of graft-derived appendicular muscles could be observed, was recently challenged. Although several studies had already suggested that myogenic precursors in the somite could also have positional identity (Donoghue et al., 1992a,b; Grieshammer et al., 1992; Murakami and Nakamura, 1991) only Alvares and coworkers clearly showed that the ability to generate either migratory ($Lbx1^+$) or non-migratory ($Lbx1^-$) muscle precursors is dependent upon intrinsic properties of the somite from which they were derived (Alvares et al., 2003). These studies also showed that the limbs contain a potent signaling mechanism (i.e. FGFs) that can override the non-migratory program of flank somites and induce expression of the migration marker Lbx1. Furthermore, the somitic predisposition toward a particular myogenic program (migratory or non-migratory) was shown to depend, directly or indirectly, on *Hox* genes. These findings show that results obtained by heterotopic grafting into the limb area (Christ et al., 1977) do not necessarily apply to other axial levels and conclusively demonstrate that the axial identity of the somites, conferred by *HOX* genes, can also determine the fate of skeletal muscle precursors. Recent data from our laboratory demonstrate that embryonic myoblasts isolated from different positions along the antero-posterior axis are characterized by a pattern of Hox genes expression very similar to that documented for whole somites (Biressi et al., 2007), clearly indicating that, in vivo, embryonic myoblasts express themselves a HOX code and thus presumably possess direct positional information. In contrast, fetal myoblasts do not express Hox genes and are probably oriented by pre-existing primary fibers (Cossu and Biressi, 2005).

Lateral asymmetry in skeletal muscle

The vertebrate body shows left–right asymmetry along the body axis. This is clearly evident from the organization and anatomical localization of different organs, such as heart, stomach, intestines, liver and lungs (Capdevila et al., 2000). Skeletal myogenesis is generally thought to occur symmetrically. Although differences in the strength and size of muscles between the right and left are well known in humans (Chhibber and Singh, 1970), this is probably the result of training and lifestyle and not a developmental process. However, Golding and colleagues recently reported asymmetric expression of *myosin light chain 3F (MLC3F)*, *α-skeletal actin* (Golding et al., 2004a) and heparin-binding EGF-like growth factor (Golding et al., 2004b) during the generation of the primary myotome. Their asymmetry is transient and not maintained during primary myogenesis and although the significance of this finding remains unclear, it suggests that some left–right asymmetry may also be involved in skeletal muscle development.

Evolutionary conservation of skeletal muscle development

The formation of muscle through the sequential appearance of different myoblast populations and leading to the generation of different types of fibers is generally conserved among amniotes (Draeger et al., 1987; Picard et al., 2002 and references therein). Nevertheless, some differences between species can be identified. For example at least three subtypes of embryonic myoblasts are present in birds (Miller and Stockdale, 1986), whereas only a single type of embryonic myoblast has been identified in mammals (Vivarelli et al., 1988). Furthermore, in birds, all of the myogenic cell lineages are, under appropriate conditions, clonogenic in culture whereas in rodents, satellite cells are the only myogenic cells with sufficient clonogenic capacity to allow them to be expanded *in vitro* as a pure population. Moreover, a subset of avian (but not mammalian) extrafusal fast fibers tend to retain their developmental MyHC isoforms (Crow and Stockdale, 1986). There are also qualitative and quantitative differences in the way muscles are formed in small and large animals. For example, it has been proposed that in man, cattle, pigs and sheep (but not in mice) secondary myotubes act as a scaffold for the formation of a third generation of tertiary myotubes, which arise in the late fetal or early postnatal period (Draeger et al., 1987; Picard et al., 2002). The

origin of these tertiary myotubes is currently unknown although satellite cells are likely to be involved. Notably, similar differences have also been reported between different muscles in the same species: for example, in the rat, tertiary myotubes have been described in intercostal (Kelly and Zacks, 1969), but not limb muscles (Ross et al., 1987).

The majority of studies on muscle development in amniotes have focused on rodents or chick. This is due to the embryological manipulability of the chick and the availability of mutants in the mouse. Moreover, it is likely that the developmental strategies observed in rodents are similar to those adopted by other mammals, including humans. Nevertheless, several studies have highlighted the value of other, non-mammalian animal models in developmental studies. In particular zebrafish (*Danio rerio*) and *Xenopus laevis* are particularly useful for practical reasons including ease of genetic manipulation, the large numbers of embryos/larvae that can be obtained and optical clarity which allows cell movement to be observed in real time. Skeletal muscle development in *Xenopus* and zebrafish shares several commune features with that observed in amniotes. All share multistep muscle development, involving the appearing of different classes of myogenic progenitor which give rise to fibers with different contraction characteristics (Barresi et al., 2001; Chanoine and Hardy, 2003; Devoto et al., 1996). Other similarities include the formation of a dermo/myotome and the strategies involved in the formation of limb/fin muscles (Devoto et al., 1996, 2006; Hollway and Currie, 2005; Neyt et al., 2000). Moreover, also signals that drive the specification and differentiation of myogenic cells appear to be, at least partially, conserved in vertebrates (Chanoine et al., 2004; Chanoine and Hardy, 2003; Coutelle et al., 2001; Grimaldi et al., 2004; Hoppler et al., 1996). Conversely, although different types of myoblasts have also been identified in invertebrates, muscle development is profoundly different from that observed in vertebrates (Baylies et al., 1998). Apart from some intriguing similarities in certain general regulatory mechanisms and transcriptional networks (Luo et al., 2005; Relaix and Buckingham, 1999), genetic analyses of invertebrate homologues of factors known to have a specific role in vertebrate myogenesis have revealed an evolutionary functional divergence, suggesting that fundamental mechanisms involved in invertebrate muscle development often cannot be easily translated to vertebrates (Baylies and Michelson, 2001).

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