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REVIEW

# The myogenic transcriptional network

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**Abstract** Myogenesis has been a leading model for elucidating the molecular mechanisms that underlie tissue differentiation and development since the discovery of *MyoD*. During myogenesis, the fate of myogenic precursor cells is first determined by Pax3/Pax7. This is followed by regulation of the myogenic differentiation program by muscle regulatory factors (Myf5, MyoD, Myog, and Mrf4) to form muscle tissues. Recent studies have uncovered a detailed myogenic program that involves the RP58 (Zfp238)-dependent regulatory network, which is critical for repressing the expression of inhibitor of DNA binding (Id) proteins. These novel findings contribute to a comprehensive understanding of the muscle differentiation transcriptional program.

**Keywords** Myogenesis · Pax · MyoD · RP58 · Ids

## Introduction

Vertebrate skeletal muscle is derived from the somites, which are established as paraxial mesoderm beside the neural tube and notochord (Fig. 1a) [1]. The somite progressively subdivides into two compartments, the dorsal dermomyotome and ventral sclerotome (Fig. 1b). The dorsal dermomyotome further splits into the dermatome and myotome in later stages of development to produce the trunk dermis and muscles, respectively. Myogenic precursor cells undergo an epithelial-mesenchymal transition (EMT) in response to signals from environmental cues, delaminate from the dermomyotome, and accumulate underneath to form the myotome (Fig. 1c) [2].

The dermomyotome can also be divided into dorsal (epaxial) and ventral (hypaxial) portions, though no obvious morphological epaxial-hypaxial boundary exists. Sonic hedgehog (SHH) secreted from the floor plate and notochord specifies the epaxial dermomyotome, and gives rise to the epaxial myotome that forms the back muscles [3]. The hypaxial dermomyotome is specified by signals from the dorsal ectoderm (Wnt pathway) and the lateral plate mesoderm (Bmp4), and produces the hypaxial myotome that forms the limbs, diaphragm, and body wall muscles (Fig. 1b, c) [4].

All myogenic precursor cells in the dermomyotome express the paired-homeodomain transcription factor, *Pax3* [2]. When myogenesis begins, *Pax3* expression gradually decreases, and expression of basic helix-loop-helix (bHLH) transcription factors known as muscle regulatory factors (MRFs), such as *Myf5*, *MyoD*, *Myog*, and *Mrf4*, significantly increases [2]. These cells are then specified as myoblasts, fuse with each other, and finally differentiate into skeletal muscle fibers.

Gene targeting analysis using mouse models over the last 2 decades have shown that among these MRFs, Myf5 and MyoD are critical for myoblast determination and exhibit redundant functions. Although inactivation of either gene alone has no effect on skeletal muscle phenotype at the embryonic stage, *Myf5/MyoD* double knockout (DKO) mice have a complete lack of myoblasts and skeletal muscle throughout the body [5]. In contrast, Myog is a transcription factor that plays an essential role during muscle differentiation. Indeed, while myoblasts are specified normally in *Myog* KO mice, they cannot differentiate

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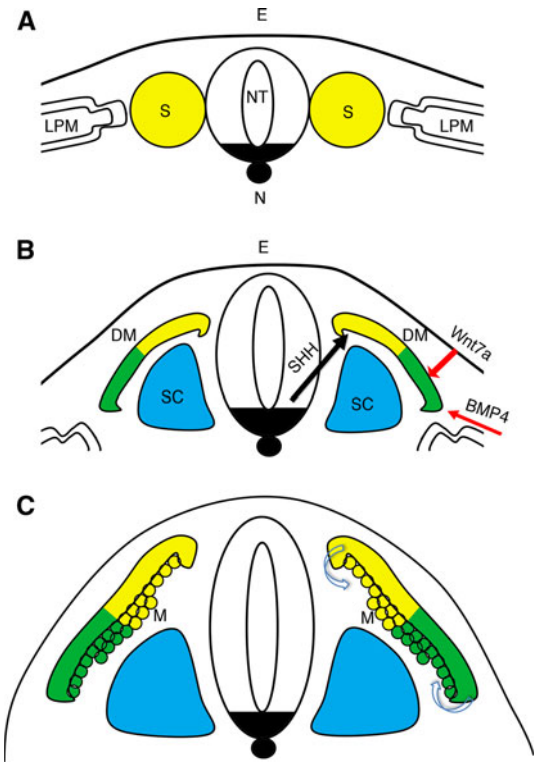


**Fig. 1** A schematic representation of somite patterning. **a** Each somite (S) forms beside the neural tube (*NT*) and notochord (*N*), adjacent to the lateral plate mesoderm (*LPM*). **b** The dorsal portion of the somite differentiates into the dermomyotome (*DM*), while the ventral quadrant gives rise to the sclerotome (*SC*). Signals from the floor plate and notochord (SHH) then specify the epaxial portion of the dermomyotome (*yellow*). Signals from the surface ectoderm (*E*; Wnt7a) and lateral plate mesoderm (BMP4) specify the hypaxial dermomyotome (*green*). **c** The two dermomyotome regions each produce a compartment of the myotome (*M*). The epaxial myotome forms from the epaxial lip of the dermomyotome (*yellow*), while the hypaxial myotome forms from the hypaxial lip (*green*)

into myotubes [6, 7]. Myog is considered a direct downstream target of Myf5 and MyoD in the muscle gene network, and other MRFs cannot compensate for the defect [6, 7]. Mrf4 was first suggested to have a redundant function with Myog under the control of Myf5 and MyoD [8], but recent studies have shown that Mrf4 functions as a determinant of myogenic lineage in the early myotome (primary myogenesis) [9].

The early myotome possesses a distinct lineage that arises through the division of epaxial and hypaxial myotome regions. The epaxial myotome is formed by myoblasts derived from the dorsomedial lip of the dermomyotome. These myoblasts first express *Myf5*. On the other hand, the hypaxial myotome is formed by myoblasts derived from the ventrolateral lip of the dermomyotome. These myoblasts predominantly express *MyoD* (Fig. 1b). Though both *Myf5* and *MyoD* single mutant mice show relatively normal muscle phenotypes, other abnormalities have been observed. *Myf5*−/− embryos show normal muscle development in the limb buds, but markedly delayed development of epaxial muscles. In contrast, while *MyoD*−/− mice display normal development of epaxial muscles, the development of limb muscles are significantly delayed. These results indicate that, even in the early myotome, at least two distinct myoblasts specified by the Myf5 and MyoD pathways exist and play different roles in muscle development [10].

## Limb muscle development

While the hypaxial dermomyotome in the flank (inter-limb) elongates as epithelial sheets that give rise to body wall muscles and intercostal muscles, the hypaxial dermomyotome cells in the adjacent limb regions leave the epithelial structure after EMT and begin migrating towards their destination, i.e., the fore- and hind-limb bud mesenchyme [11]. These long-range migratory myogenic precursor cells express *Pax3*, retain their proliferative state, and do not express MRFs during the migration (Fig. 2a). After they reach the target destination, dorsal and ventral muscle-forming regions in the limb bud begin to express MRFs, downregulate Pax3, and finally differentiate into muscle fibers [2]. *Splotch* mutant mice, which lack functional Pax3, are devoid of all limb muscles because of defects in the migration of precursors from the somites to the limb bud [12].

The key molecules involved in EMT of these myogenic precursor cells are hepatocyte growth factor/scatter factor (HGF/SF) and its receptor, c-Met [11]. These migratory myogenic precursor cells in the hypaxial lip of the dermomyotome express *c-Met* in addition to *Pax3* [11, 12] (Fig. 2B). In contrast, *HGF/SF* mRNA is predominantly expressed in the adjacent limb mesenchyme [11, 13]. Both *c-Met*−/− and *HGF/SF*−/− mice have muscle-free limbs, resembling the *Splotch* phenotype, due to the lack of myogenic precursor cell migration from the dermomyotome to the limb [11, 14]. c-Met is considered a downstream target of Pax3 because the *Splotch* mutant shows a loss of *c-Met* expression in the hypaxial dermomyotome [12]. However, it is unclear whether c-Met is a direct Pax3 target in vivo [15] and if these *c-Met* (+) precursor cells have a chemotactic response to HGF/SF [11, 13, 16].

Long-range migratory myogenic precursor cells are generated only in the occipital, cervical, and fore- and hindlimb levels of the dermomyotome ventrolateral lip. These precursors specifically express the *Lbx1* homeobox transcription factor (Fig. 2b) [17]. *Lbx1* inactivation leads to the lack of dorsal muscle mass in the forelimb and all

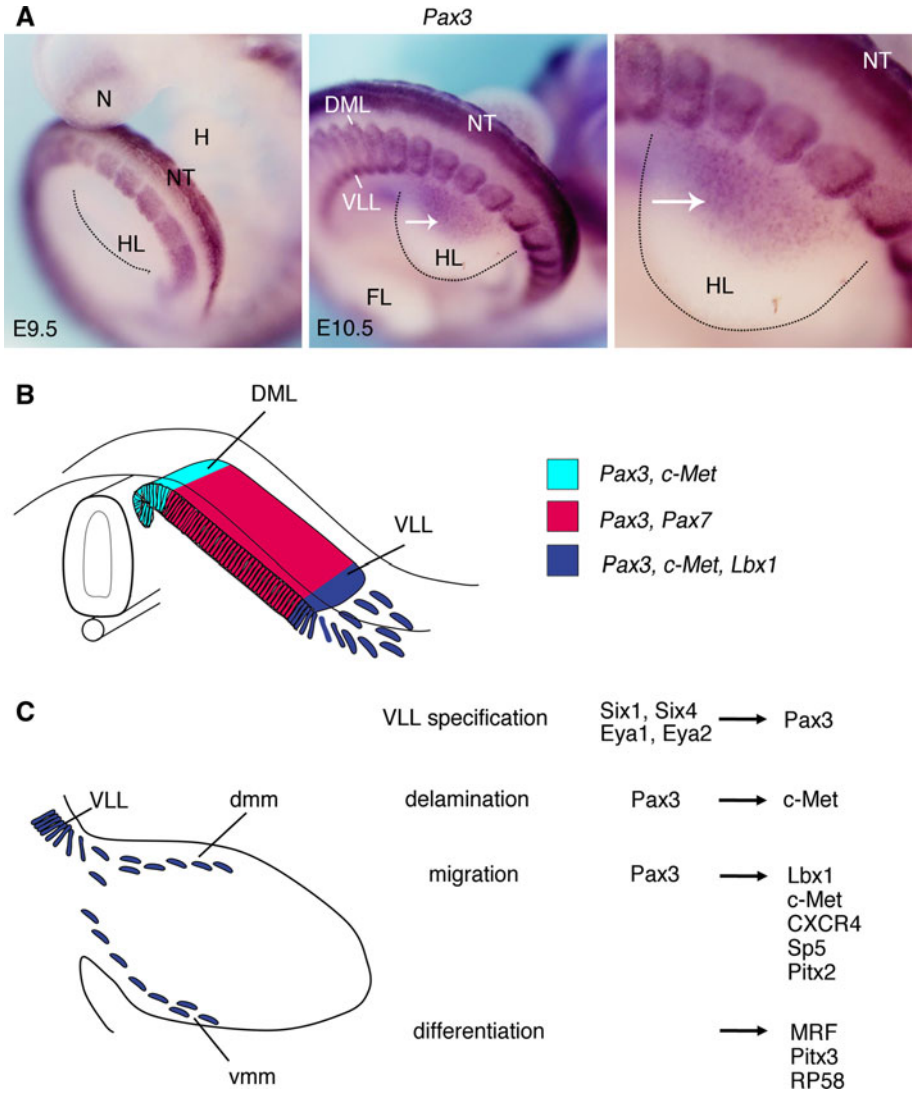


**Fig. 2** **a** Pax3 expression in the mouse embryo. *Pax3* mRNA is not detected in the hindlimb at E9.5. The *dashed line* outlines the hindlimb bud. *Arrows* mark *Pax3* (+) cells that have migrated into the limbs of the E10.5 embryo. The right panel is an enlargement of the central panel. Labeled structures are the dorsomedial lip of the dermomyotome (DML), ventrolateral lip of the dermomyotome (VLL), forelimb (FL), hindlimb (HL), neural tube (NT), heart (H), and nasal pit (N). **b** Schematic representation of the expression patterns of genes involved in dermomyotome development. *Blue cells* indicate myogenic precursor cells migrating to the limb bud. **c** A model of genes responsible for the development and migration of myogenic precursor cells to the limb bud. The migrating myogenic precursors delaminate from the VLL and populate in the dorsal (dmm) and ventral muscle masses (vmm) in the limb bud. Six1/4, Eya1/2, and Pax3 are indispensable for the specification of myogenic precursor cells in the ventrolateral lip of the dermomyotome. c-Met is important for the delamination of VLL cells. Migrating myogenic precursor cells express Pax3, c-Met, Lbx1, CXCR4, Sp5, and Pitx2. Muscle differentiation within the limb is controlled by the expression of the MRFs, Pitx3, and RP58

muscles in the hindlimb. In this mutant, *c-Met* (+) migrating precursors are correctly specified and delaminate from the ventrolateral lip of the dermomyotome, but cannot enter laterally into the limb bud [11]. These results suggest that Lbx1 is important for migratory myogenic precursor cells to find the correct guidance cues to the limb bud. It is not known why precursors of the ventrolateral lip of the inter-limb region, which express both *Pax3* and *c-Met*, can exclude *Lbx1* expression.

## Other genes expressed in migratory myogenic cells

Six family transcription factors (Six1, Six4) and Eya transcriptional cofactors (Eya1, Eya2) are also critical for hypaxial muscle specification and the migration of hypaxial myogenic precursor cells from the somites to the limb. In both *Six1/Six4* and *Eya1/Eya2* DKO mice, *Pax3* is absent from the hypaxial dermomyotome, resulting in severe defects of precursor cell migration into the limb bud

(Fig. 2c) [18, 19]. This indicates that Six and Eya proteins function as upstream regulators of Pax3 during the establishment of the hypaxial dermomyotome.

*Sp5* is expressed in the dorsomedial and ventrolateral lips of the dermomyotome, overlapping with the expression pattern of Pax3 [20]. *Sp5* mRNA is also detected in migrating myogenic precursor cells from the dermomyotome to the limb, and its expression is not detected in *Splotch* mice, suggesting that Sp5 is expressed in migratory muscle precursors and its expression is regulated by Pax3 [20] (Fig. 2c).

*Pitx2* and *Pitx3* are also expressed in limb muscles (Fig. 2c) [21]. *Pitx2* is expressed in migratory myogenic precursor cells, whereas *Pitx3* can be seen during muscle differentiation. *Pitx3* mutant mice show upregulated and prolonged *Pitx2* expression, suggesting that Pitx2 and Pitx3 may be partially redundant [21].

Recent studies have shown that the chemokine receptor *CXCR4* is also expressed in migratory myogenic precursor cells (Fig. 2c) [22]. The CXCR4 ligand, stromal derived factor 1 (Sdf1), is specifically expressed in the middle mesenchyme of the limb bud, which is the final destination of these migratory cells. Ectopic *Sdf1* expression in the chick limb bud causes an aberrant accumulation of *CXCR4* (+) myogenic cells near the source. In *CXCR4−/−* mice, fewer progenitor cells reach the limb bud and apoptosis increases, suggesting an important role of CXCR4 for migratory cues and cell survival [22]. *CXCR4* genetically interacts with *Gab1*, the adaptor molecule that mediates interaction with the c-Met receptor. In *CXCR4/Gab1* DKO mice, the number of migratory myogenic cells reaching the forelimb is significantly reduced compared to each single mutant, suggesting that a threshold number of precursor cells reaching the limb is necessary to compensate for muscle defects [22].

## PAX transcription factors and the specification of myogenic precursor cells in gastrulation and adults

Myogenic precursor cells in the dermomyotome also express *Pax7*, the analog of *Pax3* [2]. *Pax3* positive precursor cells accumulate in the dorsomedial and ventrolateral lips of the dermomyotome during development (Fig. 2a, b), while *Pax7* expression is more prominent in the central region of the dermomyotome [23, 24].

In the adult body, muscle growth and regeneration events depend on the proliferation and differentiation of muscle stem cells, termed satellite cells, which are located under the basal lamina of muscle fibers. These satellite cells express Pax7 and are mitotically quiescent in undamaged muscle. Upon injury, they are activated, migrate to the injured area, proliferate, and fuse with each other to replace degenerated muscle fibers. This is accompanied by upregulation of MRFs and the downregulation of Pax7. In *Pax7−/−* mice, satellite cells progressively die by apoptosis after birth, and *Pax3* cannot compensate [25]. Recent findings suggest that *Pax3* is also expressed in many, but not all, satellite cells [25, 26]. Quiescent satellite cells also express the receptor *c-Met*, and the ligand HGF/SF is a trigger for satellite cell activation [27]. These combined results indicate that Pax transcription factors are important for the specification and maintenance of muscle progenitor cells both in early somites and in adult muscle tissues, and suggest that a very similar transcriptional network is orchestrated during embryonic skeletal muscle formation and adult muscle regeneration.

A population of skeletal muscle progenitor cells resides in the central dermomyotome that expresses both *Pax3* and *Pax7* [28, 29]. These *Pax3*(+)*Pax7*(+) cells are mitotically active, do not co-express MRFs after entering the myotome, and persist in all fetal and neonatal muscles [23, 24, 26]. *Pax3/Pax7* DKO mice show some early embryonic muscles of the myotome, but completely lack further muscle development because of loss of the muscle progenitor cell population [26]. Cells failing to express Pax3 or Pax7 either die or assume a non-myogenic fate. These results indicate that Pax3(+)Pax7(+) mitotic progenitor cells are responsible for fetal muscle growth (secondary myogenesis) and contribute to satellite cells of postnatal mice, suggesting that embryonic muscle progenitors and satellite cells are commonly derived from the central dermomyotome [24, 26].

## MyoD and muscle differentiation

Weintraub's discovery of *MyoD* in 1986 shed new light on the molecular nature of skeletal muscle differentiation [30]. Weintraub's group cloned *MyoD* by subtractive hybridization from azacytidine-treated myoblasts (by subtracting cDNA of azacytidine-induced myoblasts from mouse 10T1/2 fibroblasts) and demonstrated that *MyoD* alone was enough to convert 10T1/2 fibroblasts into myoblasts [31].

MyoD (as wells as other bHLH MRF factors) binds the E-box sequence (CANNTG) in promoters of downstream muscle target genes, thereby driving the transcription of these muscle-related genes in collaboration with myocyte enhancer factor 2 (Mef2) transcription factors (Fig. 3a) [32]. Mef2C is specifically expressed in muscle tissues and binds to DNA near E-boxes. Normally, these bHLH MRFs dimerize with E-proteins (E12, E47 and HEB), which are ubiquitous throughout the body, to activate downstream gene expression [32]. However, in the presence of inhibitor of DNA binding (Id) proteins (Id1–Id4), which are negative

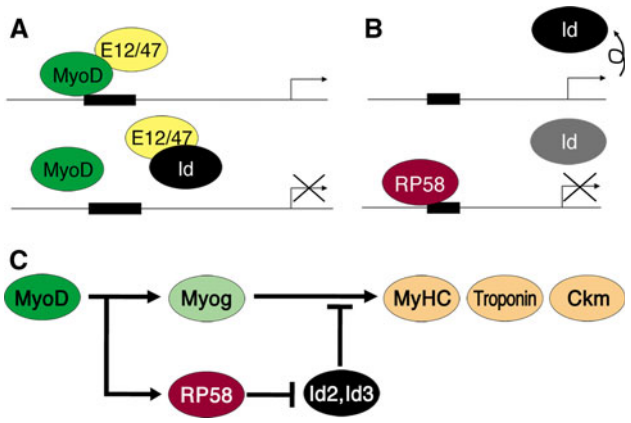


**Fig. 3** MyoD activates target gene expression. **a** MyoD dimerizes with E2A and binds to the E-box in promoters of muscle-specific genes. Id proteins prevent the formation of MyoD/E2A heterodimers and their DNA-binding activities. **b** RP58 represses *Id2* and *Id3* transcription by binding to the putative RP58 binding site in the *Id2* and *Id3* promoters. **c** Proposed myogenesis regulatory network via RP58

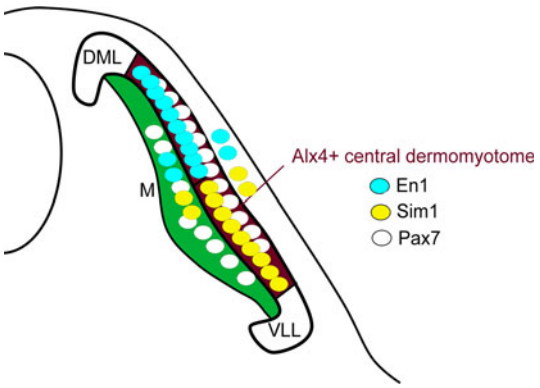


**Fig. 4** *En1* and *Sim1* are broadly expressed in the epaxial and hypaxial compartments in the somites, respectively. *Pax7* (+) *and Pax3* (+) cells predominantly reside in the central portion of the dermomyotome, overlapping with *Alx4* expression, and retain this expression even after migrating to the myotome (M). *DML* dorsomedial lip, *VLL* ventrolateral lip of the dermomyotome

regulators of myogenesis, MyoD cannot activate the transcription of downstream target genes [33]. Ids can heterodimerize with E-proteins (and to a lesser extent with MyoD), thereby attenuating MyoD function (Fig. 3a). Although the molecular mechanisms regulating the inhibition of Id protein expression are unknown, we recently found that the transcriptional repressor RP58 (mouse Zfp238) is expressed in early differentiated muscle tissue and represses Id2/Id3 expression, allowing MyoD to promote muscle differentiation (Fig. 3b) [34]. *RP58* is first expressed in limb muscle tissues around E11.5, coincident with *Myog*, and like Myog, is upregulated by acetylated MyoD during early differentiation stages [34, 35]. These results indicate that MyoD both activates (via Myog) and represses (via RP58) a distinct gene set that permits the progression of skeletal myogenesis to late differentiation (Fig. 3c) [34, 36].

## Future directions

Expression of the aristaless-like homeobox transcription factor *Alx4* demarcates the central region of the dermomyotome, excluding the dorsomedial and ventrolateral lips [37]. *En1* expression partially overlaps with *Alx4* expression in the epaxial portion of the central dermomyotome and is adjacent to expression of the bHLH transcription factor *Sim1*, which is expressed in the hypaxial portion of the central dermomyotome that overlaps with *Alx4* [37]. Using fate mapping analysis in the mouse embryo, Atit et al. [38] demonstrated that *En1*-expressing central dermomyotomal cells have three distinct fates: dorsal dermis, epaxial muscle, and, unexpectedly, some interscapular brown fat. In addition, Ben-Yair et al. [39] showed that a single cell in the central dermomyotome has the potential to produce both myotome and dermatome cells by asymmetric cell division. It is noted that *En1* and *Sim1* are expressed not only in the dermomyotome, but also in the adjacent myotome and dermis (Fig. 4). These results imply that multipotent common progenitor cells that reside in the central dermomyotome region can also express *Sim1*. Moreover, these central dermomyotome cells are also *Pax3* and *Pax7* positive in early development (Fig. 2b, 4). It was previously shown that *Pax3* and *Pax7* positive cells derived from the central dermomyotome are also found in adult muscle satellite cells beside the myotome, indicating that muscle satellite cells have a common origin with embryonic myogenic precursor cells in the dermomyotome of somites [24, 26]. Therefore, En1 may contribute to the specification of adult muscle satellite cells, although its expression in these cells has not been reported.

Recent studies have shown that brown fat cells are derived from skeletal muscle lineage progenitor cells. It was previously thought that white fat cells and brown fat cells have a common adipogenic origin. However, through in vivo cell tracing analysis, Seale et al. showed that brown fat cells are derived from Myf5 (a skeletal muscle-specific transcription factor) positive muscle cells during early development [40]. They also showed that the SET domain-containing Zinc finger transcription factor Prdm16 determines the fate of these multipotent Myf5 positive precursors to become brown fat cells. This ability of Prdm16 is bidirectional. *Prdm16* knockdown in brown fat cells results in skeletal muscle-specific gene upregulation, and its overexpression in C2 muscle cells causes downregulation of muscle genes and brown fat formation.

Furthermore, Tseng et al. [41] found that Bmp7 can stimulate the brown adipose lineage, activating *Prdm16*, *Pgc-1a*, and the brown fat marker, uncoupling protein 1 (*Ucp1*). *Bmp7−/−* mice show a dramatic reduction in brown fat and an almost complete lack of Ucp1. In contrast, *Myog−/−* mutant mice show ectopic brown adipocytes in some regions that are normally skeletal muscle tissue [6]. This myoblast/brown adipocyte precursor may exhibit some plasticity for cell fate and can switch fates based on surrounding cues. This is very intriguing given the ability of brown adipose tissue to burn fat. However, it is currently unknown whether there are interactions between Prdm16 and Bmp7 expressing regions within the somites and central dermomyotome where brown adipocytes are produced. Further studies of the genetic interactions between *Prdm16/Bmp7* and genes expressed in the central dermomyotome, such as Alx4, En1, Sim1, Pax transcription factors, and other unknown factors, will shed light on mechanisms underlying the specification of different cell fates of central dermomyotome cells.

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