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Review

Tissue cross talks governing limb muscle development and regeneration

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ABSTRACT

For decades, limb development has been a paradigm of three-dimensional patterning. Moreover, as the limb muscles and the other tissues of the limb's musculoskeletal system arise from distinct developmental sources, it has been a prime example of integrative morphogenesis and cross-tissue communication. As the limbs grow, all components of the musculoskeletal system (muscles, tendons, connective tissue, nerves) coordinate their growth and differentiation, ultimately giving rise to a functional unit capable of executing elaborate movement. While the molecular mechanisms governing global three-dimensional patterning and formation of the skeletal structures of the limbs has been a matter of intense research, patterning of the soft tissues is less understood. Here, we review the development of limb muscles with an emphasis on their interaction with other tissue types and the instructive roles these tissues play. Furthermore, we discuss the role of adult correlates of these embryonic accessory tissues in muscle regeneration.

1. Introduction

The paired appendages of vertebrates arise from an outgrowth of the flank of the embryo. The outgrowth of the limbs is mainly carried by proliferating mesenchymal cells, which start to differentiate concomitant with the outgrowth process in a proximal to distal fashion. During this process, in a narrow time window, a morphologically indistinct mesenchyme is transformed into an elaborate array of different tissues most impressively demonstrated by the complexity of the limb's musculoskeletal system [1]. Vertebrate limbs contain approx. 40 muscles, each of a specific shape and size. Muscles are connected via their myotendinous junction to tendons, which allow transmission of force to the skeletal elements. The insertion of tendons at the bone surface often requires the formation of bone eminences enabling a tight mechanical connection. Creating such an elaborate arrangement requires global patterning system delineating the overall three-dimensional coordinates of the nascent limb bud. These coordinates are iteratively refined to allow establishing the intricate pattern and shape of the limb's structures. Equally important, it requires cross-tissue communication to enable mutual organization and finally mechanical linkage of tissues. In the limbs, the latter process receives another twist in the plot since the tissues of the musculoskeletal system are not derived from the same developmental source, as skeleton, tendons and connective tissue originate from mesenchymal cells in place, whereas myogenic cells arise from migratory progenitors that invade the limb bud.

While the molecular mechanisms underlying the myogenic process have extensively been reviewed, including recently [2,3], here we will briefly review the myogenic process in the limb and explicitly look at these processes through the lens of interactions between muscle cells and neighboring tissue-types, such as connective tissue and/or nervous tissue. Such interactions are increasingly emerging as playing crucial roles in defining muscles positions and shape, but also in promoting myogenic growth and differentiation [4–6] and in coordinating tissue forces (and the emerging force generating capacity of contractile muscle cells). These cross-talks between tissue-types matter not only during development, but are also remobilized and necessary in adult muscles for homeostasis and regeneration.

2. Limb muscle formation

2.1. Origin of tissues

All tissues of the musculoskeletal system, except nerves that derive from ectoderm, originate from the mesoderm. After its emergence during gastrulation, the mesoderm is classically partitioned into paraxial, intermediate and lateral plate mesoderm (LPM). During embryonic development, limbs appear at the flank of the embryo at discrete positions as thickening structures mainly composed of lateral plate mesoderm cells, covered by a layer of ectoderm. In the last century, the origin of tissues within the limbs has largely been explored using the

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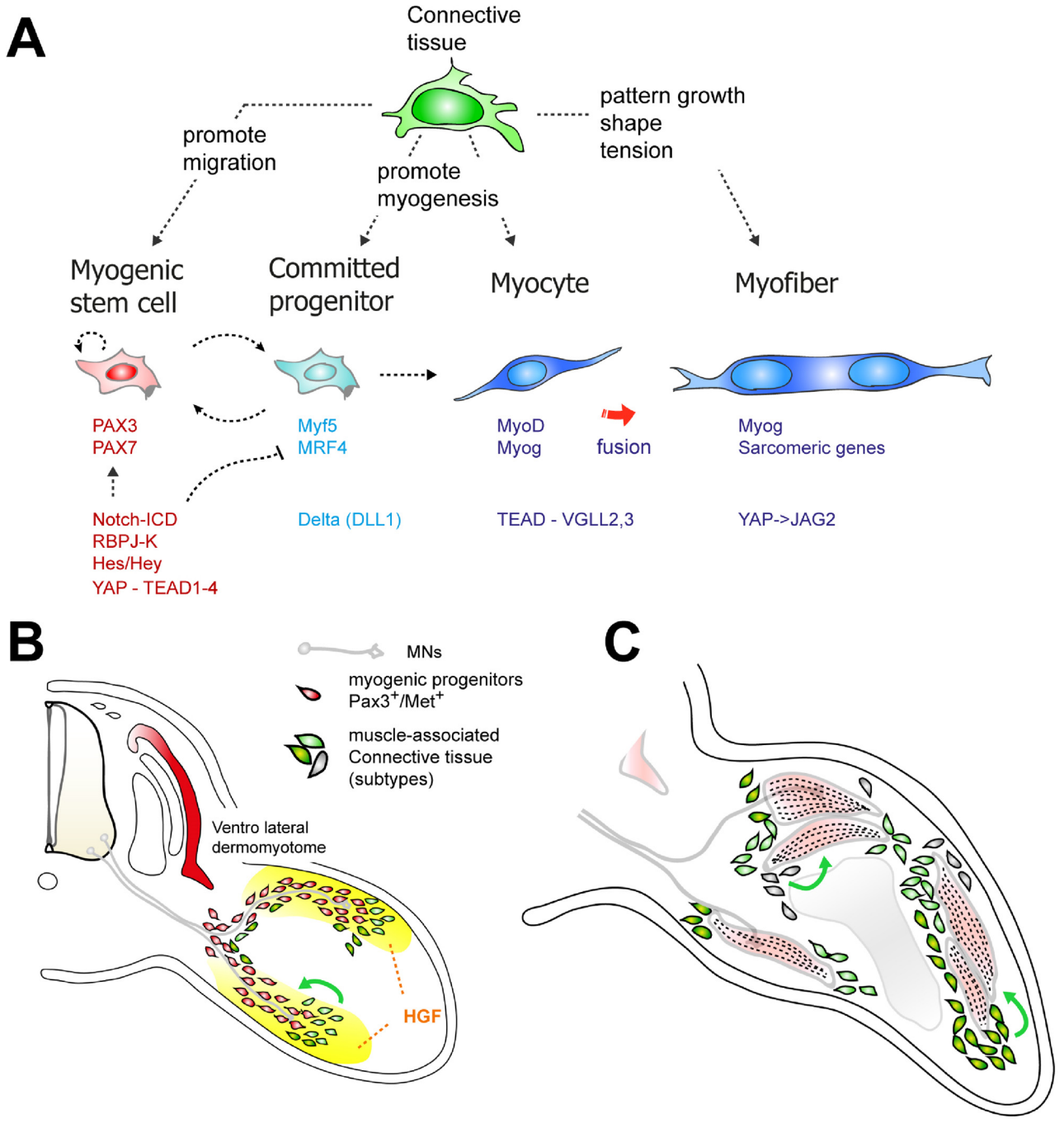

Fig. 1. Stepwise morphogenesis and myogenic differentiation of limb skeletal muscles. (A) Cellular steps of myogenic differentiation. The top row represents connective tissue cells and the types of modalities by which they influence myogenesis. The middle row represents cells at different stages of the myogenic sequence, the way they are linked, and the main molecular markers of each of these steps. The bottom row indicates the main actors participating in cellular decisions. (B, C) Schematic representation of a mouse embryo cross section at limb levels featuring two successive steps of limb muscle morphogenesis. (B) Myogenic progenitors delaminate from the ventro-lateral dermomyotome lip, and migrate through the limb bud mesenchyme, towards dorsal and ventral positions where they will coalesce into muscle masses. Green cells represent subsets of mesenchymal cells providing instructive signals influencing migration, differentiation and spatial distribution of myogenic cells. (C) Muscles receive instructive signals from various subsets of connective tissue cells allowing them to define their attachment, orientation, growth.

avian limb as an excellent model for experimental studies, owing to the possibility of performing grafts of pieces of tissues of one species into another [7]. These experiments, later supported by numerous fate mapping studies in mice [2], showed that in the trunk and limbs, the myogenic lineage was derived from the somites, segmented epithelial structures emerging from the paraxial mesoderm [8]. All other tissues in the limb bud constitute a distinct cell lineage derived from the lateral plate mesoderm [9].

2.2. Development of the Myogenic lineage

2.2.1. Specification of the myogenic lineage

Molecular determinants of myogenic differentiation comprise a set of transcription factors, collectively referred to as Myogenic Regulatory factors (MRFs), which are necessary to trigger the skeletal muscle differentiation program (Fig. 1A) [10]. These factors sequentially activate each other's transcription in a stepwise manner, whereby an initial wave of MRF4 and Myf5 expression is followed by activation of MyoD

(Myod1) expression, subsequently leading to activation of Myogenin, which acts as a main activator of a collection of genes encoding sarcomeric proteins. At this final stage of terminal differentiation, activation of myogenin (Myog) turns the cells into myocytes, which then fuse with each other to form multinucleated muscle fibers, or fuse with pre-existing fibers. Whereas there is a clear hierarchy in the molecular sequence, there is also a certain degree of redundancy between activities of these MRFs. Thus, a given MRF can compensate to some degree for the lack of another factor at a similar or neighboring level of the regulatory sequence (with compensations between Myf5, MRF4 and MyoD), whereas simultaneous deletions abrogate the program more severely [11,12].

In the trunk skeletal muscle lineage (Fig. 1A), upstream of this regulatory cascade, Myf5/MyoD-expressing myoblasts derive from cells expressing Pax3 and Pax7 [13,14], which constitute a pool of myogenic progenitors and also serve as a reservoir for adult myogenic progenitors [14,15]. Simultaneous ablation of *Pax3* and *Pax7* severely abrogates myogenic differentiation in the embryonic trunk and massively result in cell death [14]. In the developing myotome, there is a lineage continuum between cycling cells expressing the transcription factors Pax3 and Pax7, tagging them as embryonic muscle progenitors, and cells in which activation of genes of the MRF cascade coincides with extinction of Pax3/7 expression, with cell cycle exit, and with commitment to activate the myogenic program [16]. Simultaneous detection of Pax7 and Myf5 proteins reveals that at early developmental stages in murine and avian embryos, a majority of cells co-express Pax7 and Myf5 [17]. In contrast, at late fetal stages in mice, there is a mutual exclusion of Pax7 and Myf5 expression, respectively distinguishing cycling progenitors from differentiated cells, already aligned to form the future multinucleated fibers [17].

Although Pax3/7 are necessary for the early commitment to a myogenic fate, and for maintaining the progenitor fate throughout development and at late fetal stages, Pax3 is also involved in the progression towards subsequent states, by directly activating Myf5 expression [18]. The mechanism that ultimately leads to the mutual exclusion of Pax7 and Myf5 at later stages is not completely understood. Activation of *Myf5* expression marks, and is necessary for, the activation of the differentiation cascade. Consistently, inactivation of *Myf5* interferes with the progression of myogenic differentiation, and leads to the persistence of Pax3 and Pax7 expression, thus locking cells in the progenitor state [16]. This implies that Myf5 transcriptional activity, in addition to triggering expression of the MRF cascade, is also necessary for the repression of Pax3/Pax7 expression. On the opposite, maintenance of the progenitor fate by Pax3/7 at late fetal stages may involve their ability to repress Myf5, as seen in early experiments in cultured cells [19]. Likewise, in adult satellite cells, there is a mutual cross repression of Pax7 and MRF factors [20,21]. These findings are consistent with the possibility of antagonistic regulation between Pax3/7 and MRFs. Such mutual antagonism might involve direct cross-repressive transcriptional activities in the same cells (whether by antagonistic binding on the same cis-regulatory DNA regions, or by regulating antagonistic targets), or cellular cross talks between progenitors and differentiating cells, such as those involving Notch/YAP pathways (see part 2.2.3).

Distinct regulatory programs of mesoderm specification govern the development of head and trunk muscles [10,22,23]. Whereas all progenitors, irrespective of their developmental origin, start their myogenic journey by activation of Myf5 expression, the upstream events leading to Myf5 activation differ between embryonic regions. Trunk muscles essentially rely on Pax3 as the main Myf5 activator, driven by accessory regulatory impulse of Six1 and Six4 homeoproteins [24], or the transcriptional repressor RP58 [25]. In contrast, the majority of craniofacial muscles share their origin with heart muscles, and are derived from a common cardiopharyngeal progenitor [26,27], the specification of which is under the broad regulatory control of Tbx1 [28,29]. Extraocular muscles constitute another subtype of craniofacial muscles, derived from cranial mesoderm, molecular history of which starts under the umbrella of another key transcriptional regulator, Pitx2 [30].

2.2.2. Migration of muscle progenitors

Like all trunk musculature, limb muscles derive from somitic mesoderm, emerging from a region called the dermomyotome (Fig. 1B). However, they differ from other axial muscles in the sequence of molecular and morphogenetic events governing myogenesis [31]. Limb muscles emerge from the ventral dermomyotomal lip at limb levels, thus matching the definition of hypaxial muscles, a term that classically refers to the musculature derived from the ventral part of the somites [31,32]. Unlike hypaxial muscles at interlimb levels, which move from this ventral position by expansion of an epithelial-like sheet, limb myoblasts instead individualize from each other, undergoing epithelial-mesenchymal transition, followed by cell delamination from the ventral lip, and acquisition of a motile program enabling them to migrate individually over long distances across the limb mesenchyme (Fig. 1B). Whereas myoblasts are committed to be myogenic prior to this migration event, the process of myogenic differentiation only starts after their delamination, as they are on their way to their final destination.

Genetically, the regulatory program that endows limb hypaxial myogenic cells with the capacity to undergo an epithelial to mesenchyme transition and to adopt their migratory behavior is specified by Pax3 [33,34]. Aside from its key role in specifying the myogenic fate [18], Pax3 is required to transcriptionally activate expression of the Met tyrosine kinase receptor in migratory myoblasts [34,35]. Met signaling is activated by Hepatocyte growth factor (HGF), a secreted growth factor produced by the limb mesenchyme, sufficient to trigger the motility program. As a result, lack of either *Pax3* [33] or *Met* [36–38] is sufficient to abolish the migratory program and prevent the formation of limb migratory muscles, as wells as diaphragm and muscles of the tongue. Similar findings in zebrafish (where *hgf* and *met* are required for migration of appendicular muscles such as those of the fins) argue that the essential role of HGF/Met signaling is evolutionarily conserved [39,40]. Nevertheless, the co-option of HGF/Met signaling to control this migratory behavior is only found in bony fishes, and seems to have occurred after the appearance of paired appendages in cartilaginous fishes [41]. Signaling effectors of the HGF/Met signaling pathway, such as Gab1 [42], Pi3K and Src [43–45], were found to contribute to limb muscle migration.

Another key transcription factor known to specify the migratory behavior of subsets of limb myoblasts is Lbx1, the absence of which also leading to a partial depletion of limb muscles, most severely in the distal segments [46]. Owing to genetic tools allowing fluorescent tracing of *Lbx1* expressing myoblast, the comparison of differentially regulated transcriptome from *Lbx1-GFP*$^{+}$ cells sorted from limbs of control or Lbx1 mutant embryos allowed identifying additional pathways involved in controlling the motile behavior [47]. Among those, this highlighted the role of another mesenchyme-derived factor, Sdf1/Cxcl12, and its receptor Cxcr4, the expression of which is regulated by Lbx1 in migratory myoblasts [47], and which is necessary for the migration of subsets of myogenic progenitors [48]. Thus, HGF and Cxcl12 are two factors secreted by the limb mesenchyme, which cooperatively trigger and modulate myoblast motility, involving common cytoplasmic signaling effectors, such as Gab1, downstream of Met and Cxcr4 [42,47]. Their expression is preserved in the limb of embryos devoid of migratory appendicular muscles, such as Pax3 or Met mutants. Interestingly, selective overexpression of Met in the mesenchymal but not the myogenic lineage robustly interferes with myoblast migration, by blocking the release of biologically active HGF from limb mesenchymal cells [49]. The capacity of Lbx1 to trigger myoblast migration is dependent on its phosphorylation on key serine residues by Erk kinases [50]. This suggests that Lbx1 transcriptional activity might be activated downstream of an Erk-dependent signal transduction cascade, such as those modulated by HGF/Met or Cxcl12/Cxcr4, potentially explaining

why *Lbx1* inactivation only affects migratory muscles, while it preserves other Lbx1-expressing muscles.

Once motile, myoblasts migrate as streams of cells across the surrounding connective tissues, while also undergoing myogenic differentiation. Migrating myogenic cells are endowed with the capacity to navigate the molecular landscape of the limb bud, and to form muscle masses in the adequate places. Initially divided in dorsal and ventral muscle masses (Fig. 1B), these myoblast collectives will subsequently aggregate in discrete areas to form progressively smaller units, i.e. individual muscles (Fig. 1C), which may on occasion undergo a secondary splitting event [51]. During this process, myogenic progenitors receive and process positional information allowing the highly stereotyped positioning of muscles and their attachment sites within the limb, highlighting the similarity with the process of axonal guidance, which simultaneously wires motor projections towards limb muscles. Key muscle patterning signals are released by mesenchymal cells. Aside from diffusible motility signals likely acting as chemoattractants for myoblasts, such as HGF and Sdf1/Cxcl12, this process also involves contact dependent axon guidance signaling mechanisms, such as ephrinA5/EphA4 [52]. The separation of muscle masses into individual muscles coincides with the appearance of capillary sprouts between muscles marking the future cleft [53]. Furthermore, interfering with vessel growth disrupts the splitting process [53], thus assigning to growing vessels a key role in patterning muscle splitting. Upon completion of the separation process, the coordination of muscle bundle orientation, which defines the polarity of myofibers and the position of their attachment sites to surrounding cells, is permitted by signals from neighboring connective tissues, under the regulatory control of transcription factors such as Tbx5 [51].

Migration is not restricted to hypaxial appendicular muscles, but also characterizes the development of craniofacial muscles, some neck and shoulder muscles, as well as the diaphragm. Another key feature of the migration process is that collectively moving cells coordinate their polarity with that of their neighbors. This is particularly apparent during the subcutaneous progression of neck muscles, of facial expression muscles, or of subsets of shoulder muscles. Although this could be dictated by external directional cues, there are some indications that this is intrinsically regulated and may involve mechanisms analogous to planar cell polarity. Support to this possibility came from the finding that inactivation of the Fat1 Cadherin, an adhesion molecule of the Fat-like family, known to regulate tissue morphogenesis by modulation the planar cell polarity or Hippo pathways, caused alterations of subsets of migratory muscles in the face and shoulder [54]. *Fat1* ablation in the migratory lineage (driven by *Pax3-cre*) was sufficient to disperse myoblasts in the limb and to lead to the formation of supernumerary muscles in ectopic position [54,55]. So far, how Fat1 signaling controls myoblast polarity is not known. By similarity with other PCP-dependent collective migration events, it may allow migrating myogenic cells to remain in contact with each-other and to perceive the direction of migration of neighboring cells in the collective.

2.2.3. Muscle growth and balance of proliferation/differentiation

The process of developmental muscle growth is a complex task that involves a massive expansion of the progenitor pool by proliferation, and simultaneously a process of differentiation, whereby cells exit the cell cycle and sequentially activate the molecular differentiation programs. The fact that muscle progenitors have the choice between staying proliferative or exiting the cell cycle implies that a successful and steady growth involves the tight regulation of the balance between the two processes. Cell cycle exit is coupled with commitment to enter the differentiation program, follows extinction of expression of Pax3/Pax7, and coincides with completion of the MRF cascade. Thus, a Pax3/Pax7^{+} progenitor is a cell that faces a choice between three options at division stage: It can undergo 1) symmetric divisions producing two progenitors (symmetric expansion of the progenitor pool); 2) asymmetric divisions giving rise to one progenitor and a cell in which activation of Myf5 will determine its commitment to differentiation; 3) symmetric divisions producing two differentiating cells, also called terminal divisions. For these cells to distinguish between these three options, there are ample arguments involving Notch signaling fate selection pathway [56–58], and growing evidence for an additional involvement of the mechanotransduction and Hippo/Yap pathway [59–61] (Fig. 1A).

2.2.3.1. Notch signaling and muscle growth and patterning. The Delta/Notch lateral inhibition pathway is well known to organize fate selection in a group of cells with equivalent developmental potential [62,63]. By comparing signaling strength in neighboring cells, this system works by amplifying small stochastic molecular differences between cells, thereby reaching and stabilizing cells in one of two possible choices, most frequently opposing maintenance of a progenitor fate with switching to a differentiating fate. Such a system, also referred to as a bi-stable switch when viewed with the perspective of computational modelling [64], takes advantage of the Delta/Notch signaling cassette, irrespective of the type of differentiation for which these cells are committed [65–67]. Upon Delta-Notch binding, activation of the cascade involves several events of juxtamembrane cleavage of Notch by proteolytic enzymes (presenilins, furins), thus freeing the intracellular domain (Notch-ICD/NICD) from its membrane anchor, and enabling it to translocate into the nucleus, together with its partner transcription factor RBPJ-K. A cell in which the Notch pathway is active (or constitutively activated) exhibits high levels of nuclear RBPJ-K, which induces expression of the transcriptional repressors Hes/Hey. In consequence, Hes/Hey silence the expression of the Notch-activating Delta-like ligands while simultaneously blocking transcription of differentiation genes, thereby retaining cells in a progenitor state. Thus, a cell expressing high levels of one of the Delta-like ligands will activate Notch signaling in neighboring cells, ensuring that they remain progenitors and maintain low Delta expression. This in turn minimizes the level of Notch activation within the Delta-positive cell, relieving it from the Hes/Hey-mediated transcriptional repression and allowing it to activate genes of the differentiation cascade. This ensures that successful activation of Delta-ligands allows differentiation and is restricted to differentiating cells, whereas cells in which Notch pathway is activated remain progenitors.

In developing muscle, Delta family ligands are indeed expressed by differentiated cells [68,69]. Evidence for involvement of the Notch pathway came from experiments in chicken embryos, whereby excess Notch activation resulted in inhibition of differentiation although the cells were nevertheless committed to the myogenic pathway [69]. Likewise, in adult satellite cells, Notch activation is necessary to sustain Pax7 expression and self-renewal [56,70,71]. Conversely, inactivation of *Delta1* (Dll1) or of the key mediator of Notch signaling *RBPJ-K* in mice, led to the premature differentiation of myogenic cells, and to an early depletion of the myogenic pool, thus resulting in an arrest of muscle growth [68,72]. Thus, achieving muscle growth requires a fine balance in the amount of cells with active versus inactive Notch signaling, and the regulation of this balance over time. Nevertheless a transient initial pulse of Delta, provided to dermomyotome cells by migrating neural crest cells as they pass by the somites, is required to initiate myogenic differentiation in the early somites [73]. Furthermore, early Notch signaling is also involved in helping Pax3-expressing cells decide between a myogenic versus endothelial fate, and ectopic expression of NICD in Pax3-expressing cells (driven by the endogenous Pax3 locus) forces cells to adopt an endothelial fate, rather that participating to the formation of limb muscles [74].

Although myogenic differentiation is typically coupled with cell cycle exit (differentiated cells being post-mitotic), the two processes occur independently of each other [59]. Whereas Pax3/7 expressing progenitors keep proliferating [16], cells that have reached the end of the myogenic regulatory cascade (highlighted by Myog expression)

have normally stopped dividing, and have instead activated the cyclin-dependent kinase inhibitors p21/p57, which ensures their cell cycle exit and prevent re-entry [59]. Interfering with this cell cycle exit mechanism in p21/p57 double mutants does not prevent the execution of a complete myogenic cascade, as illustrated by the detection of cycling Myog-expressing cells in double mutant embryos [59], indicating that myogenic differentiation occurs independently of growth arrest. Consistent with its late onset in the myogenic cascade, a muscle-specific regulatory element of p57 is repressed in myogenic progenitors by the Notch targets Hes/Hey and activated by MRFs [59]. Thus, Notch signaling represses both myogenic differentiation and cell cycle exit.

2.2.3.2. Mechanotransduction and YAP/TAZ pathway. The Hippo/YAP pathway has also emerged as a key regulator of the balance between stemness and differentiation in the myogenic lineage, at the interface between gene regulation and mechanical forces to which cells are exposed [58,61]. YAP and TAZ are transcription factors that can shuttle between cytoplasm and nucleus. Their nuclear entry is gated by the phosphorylation of key Serine residues by serine/threonine kinases of the Hippo pathway (Mst, Lats) [58,75]: Once phosphorylated, the serine becomes a docking site for cytoplasmic interactors such as 14-3-3, which ensure their cytoplasmic retention, thereby preventing them from entering the nucleus and from regulating transcription [76]. When in the nucleus of cycling cells, YAP/TAZ are mainly known to induce expression of cell cycle genes and to maintain stemness [76,77]. In muscle progenitors (myogenic stem cells), a phosphorylation-deficient form of YAP, constitutively nuclear and transcriptionally active, was capable of blocking myogenic differentiation of C2C12 cells and increasing Pax7 expression [78,79]. In contrast, ShRNA-mediated silencing of YAP allows the cells to activate Myf5 expression and to undergo differentiation [78,79]. Within the nucleus, YAP and TAZ can interact with a wide array of transcription factors, among which the earliest-known was TEAD [77,80]. Inactivation of YAP transcriptional activity can also be achieved by disrupting its interaction with DNA-binding transcriptional partners such as TEAD factors, and this activity is efficiently mimicked by the YAP inhibitor verteporfin [77,80]. TEAD-family transcription factors indeed regulate myogenesis, an activity also modulated by additional co-factors such as the Vestigial homologs VGLL3 [81,82], and VGLL2 [83], the latter VGLL2/TEAD association also allowing functional response to mechanical overload in adult muscle [84,85]. Interestingly, the binding site for YAP/TAZ and for VGLLs on TEADs transcription factors are overlapping [81,86], implying a competition between the two cooperation modes. In vitro, presence of VGLL3 reduces binding of YAP to TEAD, implying that VGLL/TEAD binding out-competes the formation of YAP/TAZ-TEAD complexes [81]. This antagonism is coherent with their opposite activities, with YAP/TAZ-TEAD acting in progenitors to support self-renewal, whereas VGLL3-TEAD promotes myogenic differentiation. Consistently, a large proportion of their common target genes undergo opposite regulation by the two complexes [81]. Interestingly, one such oppositely regulated target is the angiomotin-like gene *Amotl2* [81]. Angiomotin-like genes are transcriptionally activated by YAP/TAZ, but mediate a negative feedback loop by sequestering YAP/TAZ in the cytoplasm, thereby antagonizing their activity [87,88]. Thus, by repressing Amotl2 expression, VGLL3 may also alleviate YAP from the Amotl2-mediated repression, and promote its transcriptional activity. This apparent contradiction may be explained by the finding that one of the isoforms of Amot was also found to promote the nuclear translocation of YAP (rather than prevent it) [89,90]. Such a mechanism could be at play in differentiating myofibers, where YAP/TAZ may contribute to the boost in gene transcription necessary for the synthesis of sarcomeric genes.

YAP/TAZ nucleo-cytoplasmic shuttling has emerged as a key sensor of mechanical forces to which cells are exposed, assigning it a role in mechano-transduction [91,92]. YAP/TAZ can be found nuclear in cycling cells grown at low density, or on stiff substrates with high tension. Conversely, they are retained in the cytoplasm when cells are confluent, or exposed to soft substrates [75,91,92]. Although the YAP pathway was originally described as ensuring progenitor maintenance and proliferation in stem cells [76,77], YAP/TAZ can also be transcriptionally active in post-mitotic or differentiated cells, when its nuclear localization is guaranteed by exposure to high tension [91,92]. This was found to occur in fetal skeletal muscles, where YAP transcriptional activity in differentiating muscle cells was shown to upregulate the Notch-activating ligands Jag2 (along with the classical YAP transcriptional targets *Ctgf* and *Ankrd1*) [57]. There, Jag2 subsequently activates Notch signaling in neighboring progenitors, thereby allowing the maintenance of the progenitor pool. Consistent with the fact that YAP activity in these cells correlates with high tension, abrogating muscle contraction in embryos (using a drug in chicken embryos, or using mouse mutants deficient for the contraction coupling channel) compromised nuclear translocation of YAP, consequently failing to activate *Jag2* expression and Notch signaling in progenitors. This leads to premature differentiation and premature depletion of the progenitor pool [57].

2.3. Patterning of limb muscles by external cues

In addition to the muscle-intrinsic signals discussed above, muscle growth and patterning is also influenced by extrinsic signals from surrounding tissues. Aside from the classical lineage studies distinguishing the somite origin of myogenic cells and lateral plate origin of the limb mesenchyme, early experiments in avian embryos indicated that muscle pattern is not encoded in the myogenic progenitors migrating to the limb buds, but rather, that local LPM-derived mesenchyme exerted an instructive role [93–96]. Intriguingly, already at this time a putative role of the extracellular matrix (ECM) secreted by local connective tissue cells was postulated [97].

A number of genetic studies have later converged towards providing additional evidence in support of this model assigning an instructive role to mesenchymal derived lineages influencing muscle development (Figs. 1C and 2 A). A number of these studies benefited from a transgenic line in which regulatory elements of the *Prx1* gene were used to drive expression of the Cre recombinase, thus allowing its use for lineage studies [98,99]. This transgene highlights all derivatives of the lateral plate mesoderm, with the *Prx1-Cre*-derived lineage encompassing all the limb mesenchyme as well as non-limb connective tissues [98]. This lineage includes all the skeletal elements (bones, tendons) and dispersed muscle-associated connective tissue cells, whereas myogenic cells do not derive from *Prx1*-expressing cells. In addition to assessing the cell autonomous requirements of many players patterning mesenchyme-derived skeletal tissues, *Prx1-Cre*-mediated deletion was also instrumental in evidencing non-cell autonomous effects on muscle development (Fig. 2B), particularly for genes with complex expression patterns (see below).

2.3.1. A brief overview of signaling systems patterning the limb bud

During early limb development, the limb bud mesenchyme, often in combination with the overlying ectoderm in form of a mesenchymal-epithelial interaction, has a crucial role in setting up the three-dimensional pattern framework (Fig. 2A). In brief, three main signaling centers define limb bud patterning: the apical ectodermal ridge (AER), the dorsal ectoderm (DE) and the zone of polarizing activity (ZPA). The ZPA, a group of mesenchymal cells located at the posterior edge of the limb bud, expresses the long-range acting morphogen Sonic hedgehog (Shh), which mediates anterio-posterior patterning in the limb [100]. The DE expresses Wnt7a, which induces the expression of the transcription factor Lmx1b in the dorsal mesenchyme [101]. Fgf8 expressed from the AER is a key factor mediating limb outgrowth; First, Fgf8 induces mesenchymal expression of Fgf10 that in turn maintains *Fgf8* expression forming a feed forward loop. Second, Fgf8 promotes proliferation and survival of the underlying mesenchyme [102]. Furthermore, AER-derived signaling participates in proximo-distal patterning

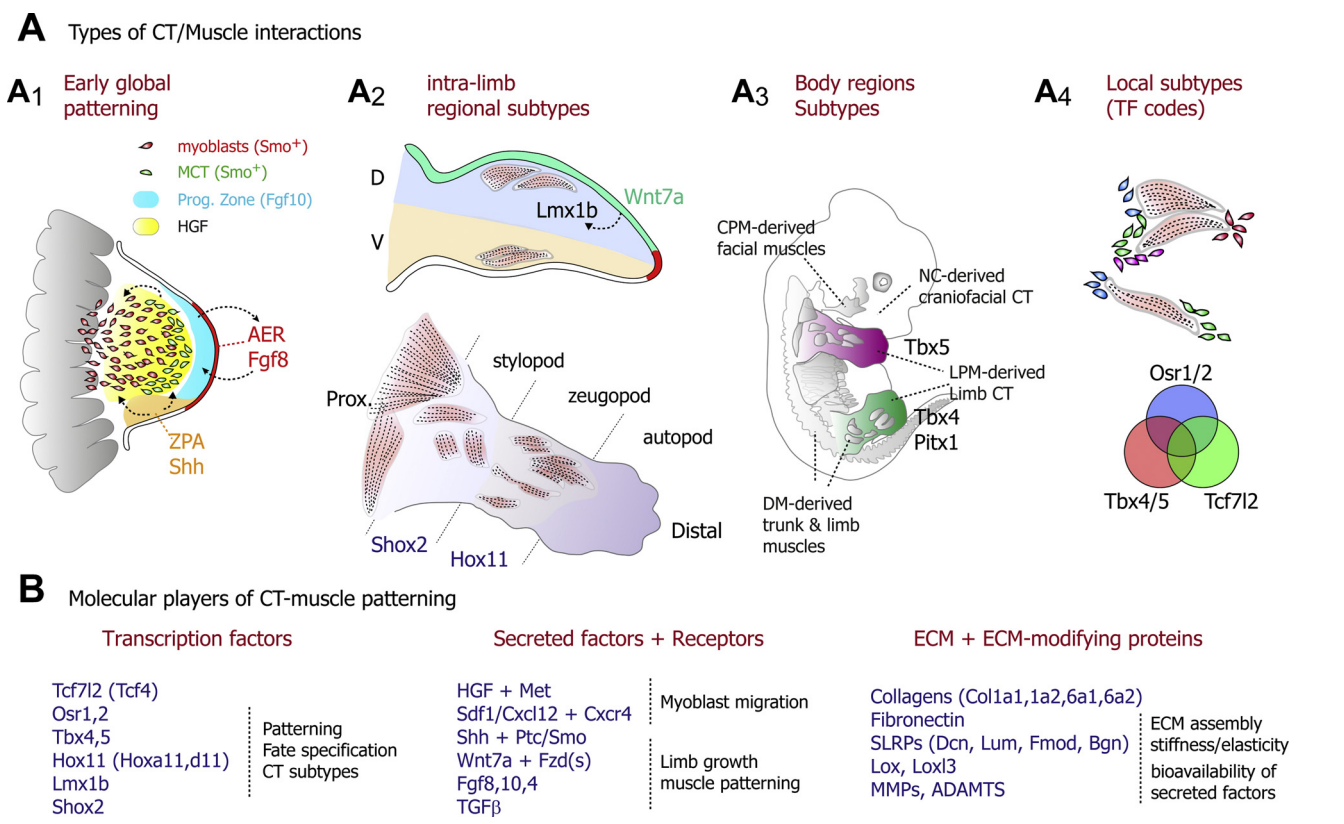

Fig. 2. Muscle-patterning activities exerted by mesenchyme / connective tissue during limb development. (A) Schematic representations of the types of patterning activities underlying: (A1) early global limb bud patterning; (A2) intra-limb local regionalization of the connective tissue along the dorso-ventral (top) and proximo-distal (bottom) axes; (A3) regionalization of connective tissues across body regions; (A4) Local diversification of CT subtypes through combinatorial codes of transcription factor expression. (B) Summary of the main molecular players and their actions. Abbreviations: AER: Apical ectodermal ridge; CPM: cardiopharyngeal mesoderm; CT: connective tissue; DM: dermomyotome; ECM: extracellular matrix; LPM: lateral plate mesoderm; MCT: muscle-associated connective tissue; NC: neural crest; TF: transcription factors; ZPA: Zone of polarizing activity.

of the limb structures, subdividing the limb into stylopode, zeugopode and autopode. The exact mechanisms governing this transition from a gradient-like signaling system to defined territories is still not completely understood, however it appears to be consensus that as a consequence each limb segment expresses specific genes of the Hox family, e.g. *Hoxa11* and *Hoxd11* genes specifically in the zeugopode. For comprehensive reviews see e.g. [103–105]. The consequences of perturbing this 3-D- limb patterning system have in the past been mainly analyzed with respect to skeletal patterning. However, not surprisingly, also soft tissue formation appears to be under this global control mechanism.

2.3.2. *Mesenchyme-derived signaling cues influencing limb myogenesis*

Shh is produced by the notochord and ventral spinal cord, as well as by the ZPA in limb bud mesenchyme. Shh had been implicated in myogenic differentiation in the chick [106–108]; in the mouse Shh non-cell autonomously acts on migrating myogenic progenitors maintaining survival and proliferation [109]. Components of the hedgehog signaling cascade (the receptors Patched (Ptch) and Smoothened (Smo), and the Gli transcription factors) are expressed not only in myogenic progenitors but also in the connective tissue. Part of Shh activity directly impinges on myogenic cells where Gli transcription factors regulate myotomal *Myf5* expression in the early somite [110], and where *Smo* is necessary for myogenic differentiation at later stages [111]. In limbs, inactivation of *Smo* in Pax3+ cells caused lack of distal muscles due to impaired migration of myogenic cells [111]. In contrast, deletion of Smoothened in the *Prx1-Cre* lineage also interfered with proper muscle patterning in limbs, inducing changes in the distribution, size, splitting and positioning of muscles [111]. Thus, by influencing connective tissue activity and limb growth, Shh non-cell autonomously acts on migrating myogenic progenitors in the limb bud maintaining survival and proliferation, but also patterning via the connective tissue [111] (Fig. 2A).

The transcription factor Lmx1b is expressed in the dorsal limb bud mesenchyme, but not in myogenic cells (Fig. 2A), and *Lmx1b* deficiency results in the mirror image duplication of ventral limb structures. *Prx1-Cre*-mediated deletion of *Lmx1b* in the mesenchyme fully reproduces these muscle patterning defects [112]. Intriguingly, deletion of *Lmx1b* in cartilage only via *Sox9-Cre* caused skeletal mispatterning but left the muscles unaltered, indicating that skeletal and muscle patterning can be uncoupled. This is in line with previous results suggesting that the skeleton develops normally in absence of muscles [113].

Hox11 genes are expressed in the zeugopode (Fig. 2A) in perichondral cells, tendons and in irregular connective tissue (ICT) including muscle-associated connective tissue [114]. *Hox* genes are well known as global regulators of limb morphogenesis and proximodistal patterning, but their function in the limb has mostly been analyzed using the skeleton as a readout [115]. Analysis of *Hoxd11/Hoxa11* compound mutants demonstrated global mispatterning of the zeugopode (i.e. the area of expression of both genes) including soft tissues such as tendons as well as muscle [114]. Also here, the effect on soft tissues could be uncoupled from skeletal patterning by leaving one allele of either *Hoxa11* or *Hoxd11* intact [114].

Prx1-Cre-mediated deletion was instrumental in distinguishing activity of the Fat1 cadherin in the mesenchyme [55], distinct but complementary to its role in the myogenic lineage [54]. This is particularly striking when following the development of a subcutaneous muscle (cutaneous maximus) emerging behind the forelimb and progressing

radially in an anterior to posterior direction. *Fat1* expression in the surrounding layer of connective tissue constitutes an increasing gradient, and its deletion in these cells robustly interfered with the progression of Pax7/Gdnf-expressing myogenic progenitors, and with the subsequent elongation of differentiated muscle fibers. Thus, *Fat1* is required for this connective tissue layer (and connective tissue associated with subsets of shoulder and facial muscles) to support both myoblast migration and myogenic differentiation [55]. As the connective tissue in the face is not derived from the LPM, but from the neural crest, severe alterations of subcutaneous facial muscles were achieved by deleting *Fat1* in the neural crest with a *Wnt1-cre* driver. This is in line with other reports uncovering an essential role of cranial neural crest-derived connective tissue in patterning facial muscles, coordinated by p53 [116,117]. These findings are interesting with regard to the identification of links between dysfunction of *FAT1* and a human muscular dystrophy affecting subsets of muscles in the face and shoulder [54,118,119], because it potentially provides a frame for understanding the basis of heterogeneity in the muscles phenotypes.

The signaling mechanisms discussed above exert complementary activities in several tissue types, e.g. in myogenic as well as non-myogenic cells, or in various LPM-derived tissues. During muscle development however, myogenic cells are most intimately associated with irregular connective tissue cells (muscle-associated CT). A number of transcription factors are expressed in the limb mesenchyme and later in irregular connective tissue, but not in the myogenic lineage. Studying consequences of their deletion for the mesenchymal lineage itself, but also for muscle patterning, provides an interesting frame to distinguish signaling cues accounting for their cell autonomous, but also non-cell autonomous functions. To this regard, the example of the transcription factor Shox2 is insightful. *Shox2* is specifically expressed in the proximal limb mesenchyme (Fig. 2A), and its constitutive deletion severely impairs limb growth, with Shox2 haploinsufficiency resulting in Short stature syndrome in humans [120]. However, analysis of early consequences of *Prx1-Cre*-mediated *Shox2* deletion, prior to the severe growth deficiency largely attributable to the lack of *Runx2*, allowed uncoupling its limb structuring role from an instructive role by which CT modulates muscle and nerve patterns [120]. Hence, its transcriptional targets uncovered in the early limb include key signals such as the Wnt modulator Rspo3 or the axon guidance molecule EphA7, and phenotypic analysis uncovered that alterations of the muscles and nerve patterns preceded growth defects occurring at later stages [120].

2.3.3. Roles of muscle-associated connective tissue

The term “connective tissue” in general defines tissues formed by fibroblastic cells that lend support to organs or other structures, together with the defined ECM that these cells produce. Connective tissue comprises a variety of subtypes, respectively termed specialized connective tissues (bone, cartilage), dense regular connective tissue (tendons) and irregular connective tissue (ICT). ICT comprises all kinds of reticular tissues including dermis and muscle connective tissue (MCT). Connective tissues of the body arise from different sources: while the CT in limbs is derived from the LPM, CT in the trunk mainly derives from the somites, and CT in the head derives from the neural crest (Fig. 2A). For a recent comprehensive review on connective tissue origin and identities, see [4,6].

2.3.3.1. Regional specificities in connective tissue activities. The transcription factors Tbx4 and Tbx5 are expressed in limb mesenchyme at very early stages and are required for limb bud initiation [121]. Later, both genes show widespread expression in limb irregular connective tissue including MCT and are required for global muscle patterning. Inactivation of either gene leads to mispatterning of limb muscles which was traced back to disrupted organization of the MCT due to defects in β-catenin-mediated cell adhesion [122]. In agreement with tissue-specific functions of Lmx1b or Hox genes, time-resolved inactivation of Tbx4 or Tbx5 also uncoupled their early role in skeletal and soft tissue patterning, respectively [122]. This altogether suggests that patterning of the skeleton and the soft tissues are mediated by in part overlapping systems that can however be executed independent of each other.

Interestingly, *Tbx4* and *Tbx5* belong to a small group of genes expressed in a limb-specific fashion: *Tbx4* is expressed in hindlimbs, while *Tbx5* is expressed in forelimbs (Fig. 2A); however they were not involved in patterning of fore-or hindlimb-specific structures [123]. This is opposed to the function of the transcription factor Pitx1, which is exclusively expressed in hindlimb mesenchyme (Fig. 2A) and controls various aspects of hindlimb-specific morphology including soft tissue patterning [124]. Interestingly, regulatory mutations at the human *PITX1* locus leading to its misexpression in forelimbs cause Liebenberg syndrome, which is characterized by a partial transformation of hard and soft forelimb structures towards a hindlimb morphology [125]. The regulatory principle behind the hindlimb-specific expression of *Pitx1* is remarkable. Expression of *Pitx1* is driven by a non-limb-specific enhancer, which however in forelimbs is actively shielded from contacting the *Pitx1* promoter by three-dimensional chromatin folding [126].

Closely related to Tbx4 and Tbx5, Tbx3 is also expressed in limb bud ICT, although in a more spatially restricted fashion. Inactivation of Tbx3, in addition to skeletal defects, caused the specific absence of two posterior forelimb muscles, the lateral triceps and brachialis, and minor defects in other forelimb muscles [127]. On a cellular level Tbx3 appeared to be required for the step of myofiber formation and orientation, however the molecular pathway downstream of Tbx3 is unknown [127]. Intriguingly, Tbx3, -4 and -5 are under control of *Hox* genes [see 121 and references therein]. This suggests that the limb mesenchyme and the tissues differentiating from it undergo consecutive steps of patterning, each leading to an increased refinement finally impinging on micromilieus governing local morphogenesis. This view is supported by a recent report showing that connective tissue cells are required for several consecutive steps during muscle bundle formation, driven by the regulatory activity of Tbx5 [51]. Both, ablation of Tbx5 in MCT via *Osr2-Cre*, as well as genetic ablation of *Osr2*-expressing MCT cells (by overexpression of DTA) severely disrupted myoblast clustering and fiber bundle orientation in limbs [51].

2.3.3.2. Muscle-specific heterogeneity of connective tissue activities. No comprehensive marker for ICT or MCT has been defined to date. Initial studies indicated Tcf7l2 (also known as Tcf4, a transcription factor downstream of Wnt/beta-catenin signaling) as a universal marker for MCT in the chicken embryo [128]. In the mouse, a majority of MCT cells appeared to express Tcf7l2 at birth [129]. However during embryonic development in the mouse, Tcf7l2+ cells are not found in all limb muscles [130]. Of note, in the mouse, also subsets of myogenic cells express low levels of Tcf7l2 [129], and Tcf7l2 is expressed in cartilage in addition to irregular connective tissue [131]. Tcf7l2 is expressed in MCT in chicken embryos independently of the presence of muscles, and was suggested to provide a prepattern for muscle formation [128]. However, in mouse emrbyos, Tcf7l2 appears to have only limited influence on muscle patterning. Tcf7l2 shows strongest expression in the elbow and knee regions, and indeed small muscle patterning defects are observed here [129]. Importantly, Tcf7l2 regulates later aspects of muscle formation as fiber maturation and fiber type [129]. Interestingly, the early expression of Tcf4 overlapping the muscle masses can be influenced by BMP signaling emanating from the most anterior and posterior mesenchyme [132].

ICT cells in avian limbs widely express the transcription factors Odd skipped-related 1 and -2 (Osr1 and Osr2) [133,134]. Osr2 appears to be more restricted to MCT than Osr1, however in chicken and mouse embryos expression of Osr2 also in myogenic cells was reported [51] [135]. In chicken micromass cultures, both Osr1 and Osr2 promote the differentiation of connective tissue cells at the expense of other tissues while knockdown reverses this effect; thus they can be ascribed an instructive role in connective tissue cell differentiation [134]. In line, loss

of Osr1 in mouse embryos leads to a transcriptional shift of the cells towards a cartilage and tendon identity, suggesting an *in vivo* requirement for Osr1 in safeguarding connective tissue cell identity [130].

In the mouse, Osr1 labels a regionalized subset of MCT cells, among other connective tissue types as e.g. dermis. Intriguingly, like Tcf7l2, Osr1 does not label MCT in all muscles; while Osr1 + cells are mostly found in superficial limb muscles, Tcf7l2 cells appear in more centrally located muscles, with varying degrees of overlap, i.e. double positive cells. We interpreted this as a hallmark of compartmentalization of connective tissue, potentially instructive for local cues shaping individual muscles [130]. In this context, the very specific defect of individual muscles in Tbx3 mutants [127] was intriguing, as it suggested the hypothesis of a "modular transcription factor code" in MCT (Fig. 2A, B) acting locally to pattern individual muscles or groups of muscles as pointed out by Sefton and Kardon [6]. Such cues may consist of secreted signaling molecules as well as ECM composition [4,6]. This principle appears to apply to Osr1: this transcription factor directly regulates the expression of locally acting signaling molecules Cxcl12 known to attract myogenic cells [47] as well as ECM genes as Col6a1 and Col6a3 [130]. *Osr1* mutants have muscle patterning defects, predominantly in muscles that show high abundance of Osr1 + cells. Affected muscles mostly displayed a truncation-like phenotype that was caused by absence or misplacement of myogenic progenitors. In addition, myogenic progenitors in *Osr1* mutants showed decreased proliferation and ectopic apoptosis leading to a decrease in myogenic cell numbers. Cultivating myoblasts on an ECM substrate produced by wild type or *Osr1*-null cells demonstrated that the microniche produced by these cells was crucial for maintaining myoblast proliferation [130]. This suggests a scenario where the locally restricted combinatorial expression of a set of transcription factors, themselves likely under control of upstream patterning mechanisms, impinges on a local microenvironment, i.e. a biochemical as well as biomechanical ECM niche that locally instructs tissue morphogenesis [136] (Fig. 2A, B). Of note, the same principle may not only apply to limb muscles, as overlapping players were identified in other muscle groups as well. Tcf7l2 is expressed in diaphragm MCT, for example [137], and Osr1 is expressed in MCT of a variety of trunk muscles and the diaphragm [130].

2.3.3.3. Activities of EMC and EMC modifying enzymes. A large part of the MCT is composed by ECM components, which include fibrillary collagens, the most abundant being Type I Collagen, and a number of proteoglycans participating in ECM assembly. As illustrated above, ECM produced by mis-specified CT cells (for example *Osr1* mutant CT cells) exhibit altered properties and composition interfering with their capacity to stimulate myogenesis in vitro [130]. However, knowledge on specific functions of individual ECM components is still lacking. Recently, Besse et al. [51] attempted to identify some of these components by exploring the regulatory changes occurring upon *Osr2-Cre*-mediated inactivation of *Tbx5*, in the limb MCT. They identified members of small leucine-rich repeat proteoglycans (SLRPs) such as Dcn, Lum, Fmod, or Bgn, expressed in dynamic and distinct patterns in the limb MCT. The expression of several of these compounds was altered in $Tbx5^{Osr2}$ mutants, suggesting that altered local expression of SLRPs may be responsible for the muscle mispatterning phenotypes observed in these mutants [51]. These proteins have established roles in matrix assembly and collagen fibrillogenesis [138]. Although their role during muscle morphogenesis has not been directly assessed, these proteins influence myogenesis, and their overexpression in muscular dystrophy is associated with excess fibrosis and is thought to contribute to disease severity [139–141].

ECM proteins undergo post-translational modifications that ultimately shape the 3D structure of the matrix depots and tune their physical properties [142]. A key aspect of ECM biological properties is its stiffness, which plays an important role during morphogenetic processes, such as collective migration of neural crest cells [143,144]. One such step affecting ECM properties is regulated by Lysyl Oxidase (Lox), an enzyme that catalyzes a copper-dependent oxidation reaction, leading to Lysine cross-linking of collagen fibers [145]. The main target of Lox-regulated cross-linking is Collagen 1, thus contributing to matrix assembly, but Lox is also responsible for oxidizing a number of extracellular growth factors, such as cytokines, thereby tuning their activities. Deletion of *Lox* in mice was shown to alter myogenesis, leading to the formation of muscles with reduced volume and shorter size, surrounded by excess amounts of MCT (while shape and size of bones and tendons were unaffected) [145]. This excess MCT deposition was attributable to an excess of TGFβ signaling, and was reverted when combining Lox-deficiency with chemical TGFβ inhibition (by in utero injection of a TGFβ antagonist). These results demonstrated that *Lox* is a negative modulator of TGFβ, and its activity is necessary to limit MCT expansion and allow muscle growth [145]. Interestingly, aside from the contribution of the secreted Lox to ECM modification, cytoplasmic Lox was recently discovered to regulate the nuclear translocation of VGLL3, thereby influencing the formation of VGLL3/TEAD complexes and subsequent regulation of myogenic differentiation [146]. Finally, other ECM-modifying proteases, such as metalloproteases of the MMP or ADAMTS families, may cooperate with Lox-like proteases to fine-tune the rigidity or elasticity of the ECM, but also to modulate activity or bioavailability of factors impacting muscle patterning, such as TGFβ [145,147]. Intriguingly, the muscle ECM is not only shaped by MCT fibroblasts, but also by the myofibers themselves. A particular case is the lysyl oxidase Loxl3, which is expressed at the tips of muscle fibers. Here, it serves to oxidize ECM fibronectin, thereby increasing integrin activation in the fiber and fostering the formation of a myotendinous junction [148].

2.3.4. Interaction of muscle with specialized and dense connective tissues

2.3.4.1. Coordinated development of muscle, cartilage and tendons. During limb development, mesenchyme in the center of the limb bud starts to condense and differentiate to form a continuous cartilaginous rod that subsequently becomes subdivided to the skeletal elements of stylopode (Humerus), zeugopode (Ulna, radius) and autopode (Hand/foot segments) by the insertion of synovial joints [149]. In chicken limb development, the complex array of muscles and tendon primordia are patterned at places prefiguring their future position relative to the skeletal elements ensuring the following formation of physical connections at correct anatomical positions [150]. As discussed above, the patterning of skeletal elements and soft tissues can be uncoupled, but there are few examples demonstrating their mutual communication during limb development. Maturing skeletal elements that have formed a growth plate express the morphogen Indian hedgehog (Ihh), which coordinates growth of the cartilage element as well as formation of the bone collar [151,152]. Furthermore, Ihh appears to act as a long-range morphogen towards muscle, enhancing myoblast survival during fetal myogenesis [153].

One of the first very detailed parallel description of muscle and tendon morphogenesis was made in the avian embryo, also carrying out a series of experimental approaches to evaluate their mutual dependency [150]. Tendon development was initiated independently of muscles and was preserved in muscle-less limbs, but required interaction with muscles in subsequent stages, which also applies to aneural limbs [150,154,155]. Intriguingly, downregulation of the transcription factor Scleraxis (Scx) in muscleless as well as in aneural limbs could be prevented by exogenous expression of Fgf4, which *in vivo* is expressed from the tips of muscle fibers close to the tendon attachment sites [155]. Similarly, in mice devoid of limb muscles, tendon initiation marked by the expression of Scx was normal, but later differentiation was altered [154,156,157]. Thus in sum, muscles are not required for limb tendon initiation, but for their differentiation. Intriguingly, the same principle applies to the head, but not the axial muscles and tendons [158]. The segments of tendons whose development is independent of muscles are those of the autopode. Once formed, even in a muscle-less limb such as the $Pax3^{Splotch}$ mutant context, these autopode

tendons persist up to fetal stages [154]. In contrast, later addition of the zeugopode tendon segments that insert at the wrist is impaired in muscle-less *Pax3*^{Splotch} limbs [154]. This discrepancy may reflect the dependency of late-developing zeugopode tendons on the force produced by muscle activity. This possibility is supported by the observation of alteration of zeugopode tendons, but unaffected autopode tendons in immobilized limbs [154]. In contrast, autopode, but not zeugopode tendon development was affected by the lack of skeletal structures resulting from mesenchymal-specific *Sox9* deletion [154]. Thus, these two sets of tendons are coordinated by distinct developmental programs.

In contrast, surgical ablation of tendon primordia in chicken limbs blurs the exclusion boundary between muscle and joint regions, leading to the ectopic invasion by myogenic cells of regions normally devoid of muscle cells [150]. Tendons adjacent to muscle tips express Bmp4, loss- and gain of function experiments in chicken embryos suggested that this contributed to fetal myofiber longitudinal growth by maintaining a pool of cycling progenitors at the distal ends of muscles [159]. An extraordinary case of mutual interdependence was demonstrated for the flexor digitorum superficialis (FDS) muscles in mouse forelimbs. This muscle group is initially formed in the autopode, but between E14.5 and E16.5 relocates to the distal zeugopode. Repositioning of FDS muscle was dependent on the presence of tendons as well as muscle contraction [160].

2.3.4.2. Mechanical integration. As muscles and limb tissues grow, they are exposed to increasing mechanical tensions, and the latter play an integral part in instructing morphogenetic events and cell fates. As soon as muscle fibers produce and assemble a functional contractile apparatus, they are capable of generating forces that are applied to all tissues within the developing limbs. Furthermore, this happens at the time when motor neurons have formed functional synapses with muscles, and start emitting spontaneous activity through bursts of action potentials [161]. Such spontaneous rhythmic activity was shown to be necessary for the modulation of motor axon guidance decisions [162,163]. As exposed earlier, the regulation of YAP/TAZ nucleocytoplasmic shuttling represents a key sensor in the mechanotransduction pathway linking perception of external forces to transcriptional modulation of cell behaviors [58,91].

Differences and asymmetries in adhesive forces applied on myogenic cells by their substrate can influence their decision of whether to undergo symmetric progenitor expansion, asymmetric division feeding myogenic differentiation, or terminal differentiation, thus influencing muscle growth [60]. In addition, although the mechanisms linking force and myogenesis may be different between vertebrates and insects, studies focusing on the development of flight muscles in drosophila indicate that mechanical tensions exerted on muscle fibers are necessary for the assembly of sarcomeric units and growth of the contractile apparatus [164]. While the initial tension is provided by surrounding cells [165], the additional force resulting from sarcomeric growth contributes to creating a feed-forward loop boosting muscle fiber volume growth.

Distinguishing the effects of muscle-derived signals from the effects of muscle-generated tension requires a context in which muscle activity is impaired. Experimental suppression of muscle contractility (achieved in chicken embryos by application of channel-blocking biochemical drugs or by limb immobilization) can be used to assess the impact of these spontaneous bursts of muscle contractions on skeletal development. In addition to preventing muscle growth by exhausting the pool of myogenic progenitors [57], chicken limb immobilization was also found to downregulate expression of Osr1 and its target Cxcl12 in the connective tissue, thereby affecting the cross-talk between CT and muscles [166]. As discussed earlier, among possible influences of such changes, the production of extracellular matrix components or ECM modifying enzymes by connective tissue [51,141,145] may confer the adequate stiffness to tissues surrounding muscles, thereby providing instructive information [142,144]. Furthermore, the analysis of muscle development in mouse embryos carrying mutations in a voltage-dependent channel necessary for excitation-contraction coupling, uncovered that suppression of spontaneous muscle activity altered late aspects of muscle patterning, such as the correct formation of tendons in the zygopode [154], or the translocation of extremities of digit muscles mentioned above [160].

In addition to the influence on its own growth, muscle activity is also required to shape skeletal patterns, in particular at the interfaces between muscles, tendons and bones [167]. Again suppression of spontaneous muscle contraction in mice has effects on tendon development [160], and on the later development of bone eminences, and of the enthesis, a mineralized fibrocartilage at the junction between tendons and bones [167]. Another dimension of the influence of spontaneous muscle contraction is related to the integration of muscles in functional circuits involving a sensory neuronal component called proprioception, necessary for the body to perceive muscle stretch and to adapt motor input. The proprioceptive circuitry involves perception of muscle tension by sensory neurons (contacting muscles at the level of structures called the muscle spindles, or golgi tendon organs) [168]. Proprioceptive neurons transmit this information to the spinal cord, by project either directly or indirectly onto motor neurons, thus inhibiting motor signal to some muscles, while allowing activation of their antagonist muscles (or vice versa). Interestingly, disruption of proprioception (achieved through genetic suppression of muscle spindles [169], or by interfering with specification or function of the corresponding proprioceptive neurons [170]) interferes with the balance of left/righ body activity and leads to idiopathic congenital scoliosis development, resulting from functional and morphological alterations of muscle-tendon-bone interfaces [171].

3. Adult muscle regeneration

Skeletal muscle has a remarkable regenerative capacity. Tissue lesions, given they are not exceeding certain limits, fully heal without detectable scarring. Nevertheless, large traumas, such as volumetric muscle loss or large-scale mechanic tissue disruption, overstretch this repair capacity and lead to fibrofatty infiltration. Intriguingly, skeletal muscle regeneration depends on the activity of tissue-resident progenitors / stem cells (myogenic and non-myogenic) that not only are descendants of their developmental counterparts, but also in many aspects recapitulate a developmental program during regeneration. Acute muscle trauma can be considered a massive disruption of the homeostatic balance that triggers a series of events involving not only local tissues but also invading cells of the innate and adaptive immune system. The sequence of events and the multitude of cells involved have been recently reviewed [172,173]. Here, we focus on the interaction of two resident stem / progenitor cell types, satellite cells and interstitial mesenchymal progenitors. In brief, tissue destruction leads to local inflammation and the establishment of a transient fibrotic tissue initially filling the void and stabilizing the tissue. This is paralleled by the activation of myogenic stem cells, which start to form new muscle fibers that continuously grow until the pre-injury status is reconstituted (Fig. 3A).

3.1. Emergence and function of satellite cells

Triggering a regenerative process upon acute injury that caused damage or destruction and degeneration of muscle fibers requires the activation of progenitor cells that are capable of either fusing to damaged fibers or forming new fibers thus reconstituting lost material. In skeletal muscle this function is accomplished by bespoke muscle specific stem cells, the so-called satellite cells (identified as SATs in Fig. 3). The name of these cells dates back to their original discovery [174], where the peculiar anatomical position of the cells was first described. Satellite cells are not located in the muscle interstitium, but are placed

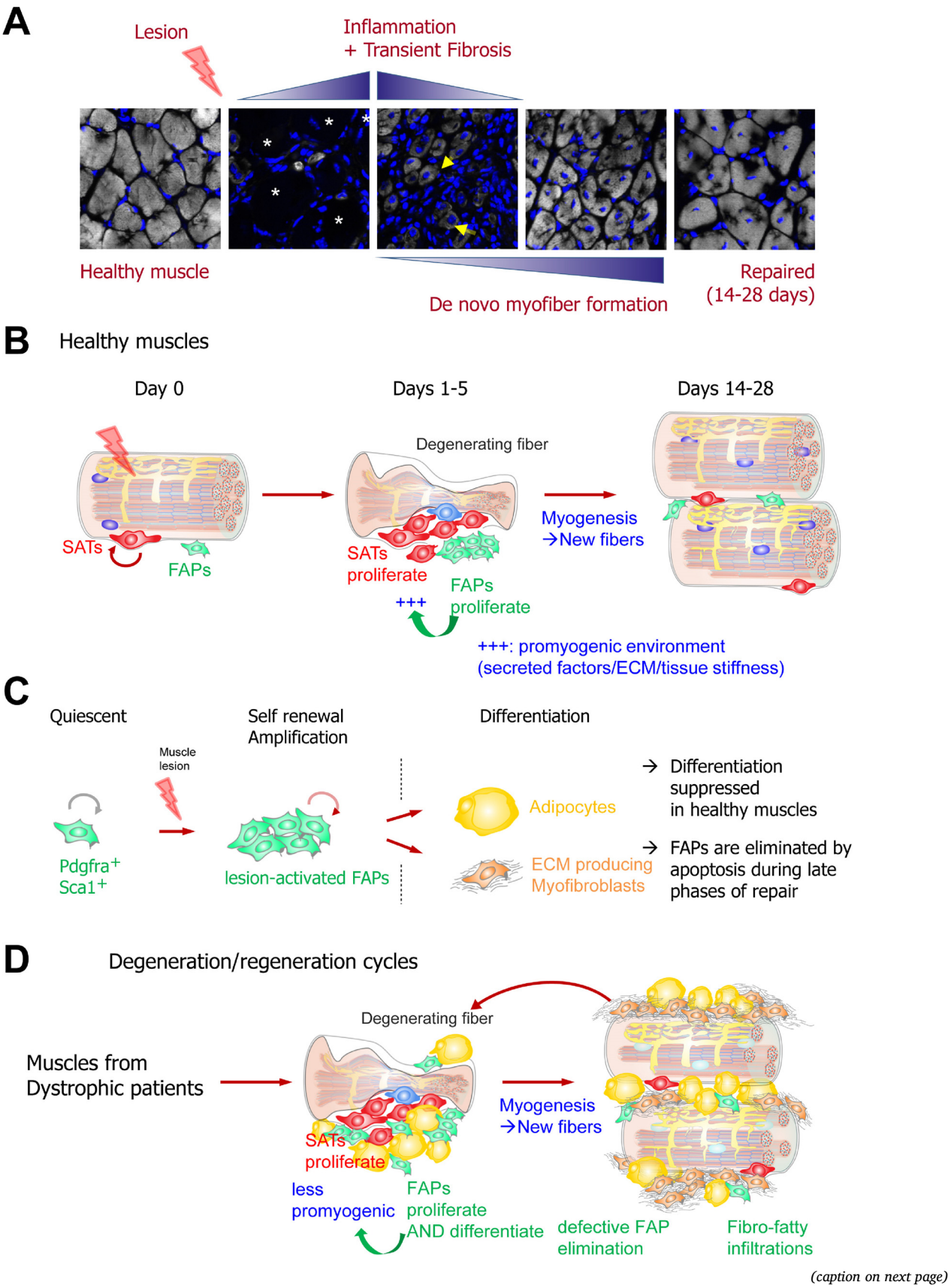

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Fig. 3. Skeletal regeneration in healthy and dystrophic muscle. (A) Aspects of muscle fibers on muscle cross sections representing the main steps of skeletal muscle regeneration upon tissue lesions, as seen by staining with Phalloidin (F-actin, white, highlighting fibers), and DAPI (nuclear staining, blue). White asterisks highlight the shape of degenerating fibers (no longer stained with Phalloidin, but still surrounded by nuclei); yellow arrowheads indicate the youngest newly formed fibers, with small diameter, recognizable by the presence of a central nucleus. (B) Schematic representation of the main cellular players and events underlying skeletal muscle regeneration in healthy muscles after tissue damage, featuring three consecutive stages, and focusing on myogenic stem cells, muscle fibers, and FAPs. (C) Differentiation potential of FAPs into adipocytes and myofibroblasts. Although FAPs have the potential to differentiate, they are mainly present as quiescent progenitors in healthy muscles, and their differentiation is suppressed. Even in the context of muscle lesions, differentiation is strictly limited and excess FAPs that initially expand after injury are eliminated by inflammatory cells, so as to free the space replenished by de novo fibers. (D) Schematic representation of the altered process of muscle repair occurring in muscles of dystrophic patients in which a context of repeated cycles of degeneration/inflammation/regeneration unleashes fibro-adipogenic differentiation and defective FAP elimination, leading to persistent fibrosis and/or adipose infiltrations.

between the basal lamina of the muscle fiber and the sarcolemma (the plasma membrane of the muscle fiber). In amniotes, adult satellite cells originate from somitic progenitors [14–16,175], meaning they derive in a lineage continuum from the same cellular source that builds up muscle fibers during development.

After a phase of massive muscle growth during fetal and early postnatal development carried mainly by fusion of progenitors to existing muscle fibers, remaining Pax7+ myogenic progenitors are subsequently withdrawn from the cell cycle and enter a state of quiescence. In mice, the vast majority of Pax7+ cells is believed to have entered quiescence at around 3 weeks after birth [176,177]. Under homeostatic conditions, most satellite cells remain in a quiescent state of dormancy, and only emerge from it in response to injury. Nevertheless, a small fraction of satellite cells participates in active turnover all during life [176–178]. Satellite cell quiescence depends on their specific niche environment, and Notch signaling has emerged as a decisive input in its maintenance [56,71]. Moreover, the extracellular matrix niche surrounding satellite cells, mainly constituted of the basal lamina in contact with integrin receptors and the dystroglycan complex, is of pivotal importance [2,179]; intriguingly, Notch signaling and cell-ECM contact are interlinked [180]. Myofibers also express Wnt4 that maintains satellite cells in a quiescent state, interestingly involving repression of YAP [181]. Besides this, interactions of satellite cells with other cell types in the environment are involved in establishing and maintaining quiescence. They are often found close to blood vessels [182]; during postnatal development, vessel-associated mural cells, so-called pericytes, secrete Angiopoietin 1 (ANG1) to promote satellite cell quiescence [183]. In adult mice, autocrine as well as paracrine ANG1/TIE2 signaling in involved in maintaining satellite cell quiescence [184].

Acute muscle injury disrupts this intricate niche environment, which in concert with other stimuli, e.g. from immune cells [172,173,185] activates satellite cells and causes their re-entry into the cell cycle (Fig. 3B). During the initial phase of muscle regeneration the satellite cell pool rapidly expands. During this process Pax7+/Myf5- satellite stem cells can undergo symmetric cell divisions forming more stem-like cells, or symmetric divisions of Pax7+/Myf5+ committed myogenic cells that expand the pool of committed progenitors. Furthermore, Pax7+/Myf5- satellite stem cells can divide asymmetrically forming one Pax7+/Myf5- and one Pax7+/Myf5+ cell thus leading to equal expansion of both pools [179,186]. Alternatively, a small proportion of committed progenitors can undergo terminal differentiation divisions, which are symmetric divisions producing two Myf5+ daughter cells in which Pax7 expression is silenced [60]. Finally, committed myogenic cells activate the differentiation program including activation of MRFs (thus recapitulating the developmental program) and finally fuse to form new muscle fibers. During this process, paralleling postnatal myogenesis, a fraction of satellite cells is withdrawn from the cell cycle and returns to quiescence in the sublaminar niche of the new fibers, thus reconstituting the quiescent stem cell pool in the regenerated muscle (Fig. 3B).

3.2. Muscle interstitial mesenchymal progenitors

Early studies pointed towards the existence of several non-satellite cell populations in skeletal muscle with varying properties [reviewed in 179]. While the relevance of most of these cell types for the endogenous regeneration process remains somewhat unclear, the past years have seen immense progress in the functional characterization of intramuscular mesenchymal progenitor cells. Muscle disease or large scale muscle trauma is often associated with replacement of muscle tissue with fibrotic tissue as well as with adipose tissue infiltration [187]. Prospective cell isolation led to the discovery of a muscle-interstitial bi-potent mesenchymal progenitor population in mice, the so-called fibro-adipogenic progenitors (FAPs), that was able to give rise to fibrotic cells or adipocytes [188,189]. FAPs are characterized by expression of the mesodermal marker PDGFRα [189], in mice as well as in human FAPs [190], and by expression of the stem cell markers Sca1 (Ly6A) and CD34 [188]. This marker profile overlaps in part with a previously characterized progenitor cell type, the PICs (PW1+ interstitial cells) that display fibrogenic, adipogenic and, if derived from juvenile mice, myogenic potential [191]. The PW1+ population was later recognized as a mix of two subtypes: a myogenic subpopulation, described as PDGFRα-; while the fibro-adipogenic population was PDGFRα+ [192]. This suggests that in adult muscle, PICs and FAPs overlap. Moreover FAPs appear to have a widespread overlap with connective tissue fibroblasts characterized by the expression of Tcf7l2 [193,194]. In line with this, fibroblasts isolated by pre-plating appear phenotypically equivalent to FAPs isolated by FACS via the above-mentioned surface markers [195]. Recent single cell studies have shed light on the composition of the intramuscular mesenchymal progenitor (IMP) pool in adult mice. Two studies [196,197] independently showed that FAPs represent the largest population of this pool, while two additional populations can be diversified. One population appears to be a tenogenic progenitor expressing e.g. Scleraxis, the second was termed smooth muscle-mesenchymal cells (SMMCs) [197], which Scott et al. [196] allocated to Pericytes. Importantly, Scott et al. identified Hic1 as a common marker for IMPs in skeletal muscle [196].

3.3. Fibro-adipogenic progenitors (FAPs) in muscle regeneration and their interplay with satellite cells

3.3.1. FAPs and myogenic regeneration in healthy muscle

In healthy muscles, FAPs reside in a quiescent state under homeostatic conditions, but are induced to rapidly expand upon muscle injury [188] (Fig. 3B, C). Quiescence of FAPs critically depends on Hic1; Hic1 is expressed in quiescent FAPs under homeostatic conditions, but declines after activation of FAPs upon acute injury. Conditional inactivation of Hic1 in homeostatic muscle disrupted FAPs quiescence. FAPs entered the cell cycle and shifted their global gene expression signature towards that of early activated FAPs. This led to a long term increase in interstitial (activated) FAP numbers, which importantly impaired muscle regeneration [196]. Of note, Hic1 appears to define a FAP-like cardiac cell type (cFAPs) that contributes to fibrosis after myocardial infarction. In line with its role in skeletal muscle FAPs, Hic1 controls quiescence of cardiac FAPs, and conditional inactivation of Hic1 causes fibrofatty infiltration in the heart [198].

Muscle injury triggers an immediate inflammatory response; cytokines released from immune cells are involved in the activation and proliferation of satellite cells [185], in addition eosinophil cell-derived Il4 activates FAPs [199]. Vice versa, FAPs appear to be a considerable

source of cytokines attracting immune cells to the site of injury [196]. Post-injury expansion of FAPs is under control of PDGFRα signaling [200]. Intriguingly, an alternative transcript derived from intronic polyadenylation leads to the expression of a truncated decoy receptor during the course of muscle regeneration thus self-limiting FAPs expansion [200]. During the course of muscle regeneration, the FAP pool temporarily expands in early phases and shrinks in later phases where excessive FAPs are removed by apoptosis [201]. In this context, an intricate interplay exists between FAPs and macrophages. During the course of injury, macrophages continuously shift their profile from a pro-inflammatory (M1) to an anti-inflammatory (M2) type. M1 Macrophages control FAP pool contraction via TNFα [201], whereas M2 Macrophage derived Tgfβ controls fibrosis [201,202]. Another recent study attributes a key contribution in the timely orchestration of these processes to FAP senescence [203]. FAP senescence occurs in response to exercise-induced damage, and is necessary to promote the pro-regenerative inflammation shift. Failure to activate senescence in chronic inflammatory myopathy leads to FAP accumulation and muscle degeneration [203].

During regeneration, FAPs appear to play a pro-regenerative, supportive function (Fig. 3B). Co-culture experiments of FAPs with myoblasts indicated a supportive role in regenerative myogenesis by expression of secreted molecules as Il6 [188]. Connective tissue fibroblasts are necessary for muscle regeneration, as diphtheria toxin-mediated depletion of Tcf7l2+ cells led to severe disruption of muscle regeneration [193]. Consistently, fibroblastic cells (likely overlapping with FAPs) also were shown to promote satellite cell survival via paracrine signaling [204]. More recently a diphtheria toxin-mediated cell depletion study was performed that exclusively targeted PDGFRα+ FAPs substantiating an essential role for these cells during muscle regeneration [205]. Furthermore, blocking FAP expansion pharmacologically via PDGFRα inhibition impaired muscle regeneration [206].

Intriguingly, much like satellite cells, adult FAPs appear to be derived from developmental progenitors; we recently showed that limb muscle connective tissue progenitors expressing the transcription factor Osr1 give rise to at least a subset of FAPs [130]. Adult FAPs do not express an Osr1-driven reporter allele, which is however resumed upon acute injury, suggesting the reactivation of a developmental program [207]. It is therefore not surprising that FAPs are generally assumed to play an assisting role during muscle regeneration by providing a beneficial microenvironment consisting of paracrine signaling cues as well as a transient pro-regenerative ECM. A very recent study elegantly confirmed this by time-resolved singly cell as well as bulk RNA sequencing [196]. For example, embryonal muscle connective tissue cells express Collagen type VI (ColVI) as a vital cue for sustaining myogenic progenitor proliferation [130], a feature apparently shared by adult FAPs. ColVI deficiency impairs satellite cell maintenance during muscle regeneration, which can be rescued by grafting of wild type fibroblasts [208]. Another ECM molecule expressed by FAPs is the small matricellular protein WISP1. Intriguingly, WISP1 expression by FAPs declines during aging, which in turn interferes with the muscle's regenerative capability [209]. Of note, in addition to providing a pro-regenerative ECM environment, FAPs may also be involved in phagocytic clearance of tissue debris [199]. Besides the supportive role for regeneration after injury discussed above, the role of FAPs in homeostatic conditions is so far not well defined. However FAP depletion under homeostatic conditions causes atrophy and drainage of the satellite cell pool, indicating a role for FAPs in maintaining myofiber hypertrophy as well as satellite cell quiescence [205]. In line with the notion that FAPs and interstitial fibroblasts mostly overlap, depletion of fibroblasts also causes muscle atrophy [210].

3.3.2. FAP dysregulation in pathological contexts

While FAPs have supporting roles in muscle regeneration their dysregulation is detrimental and can contribute to symptom severity in several pathological conditions (Fig. 3D). This may be caused by increasing fibro-fatty infiltrations, or by abrogating pro-myogenic functions of FAPs, thus compromising regeneration or causing muscle atrophy. FAPs are considered the main cellular source for fibrotic and adipogenic lesions in dystrophic muscle (Fig. 3C, D) [201,211,212], although other cell types may also contribute [213]. *In vivo*, endogenous FAPs readily give rise to muscle-interstitial adipocytes based on a pro-adipogenic microenvironment as elicited by e.g. glycerol injection [207,212]. In spite of this fibro-adipogenic potential, FAP differentiation is largely prevented in healthy muscle, whereas fibrosis or adipose infiltrations appear to be the hallmark of several muscular dystrophies including Duchenne Muscular Dystrophy (DMD) [211,214,215], Amyotropic lateral sclerosis (ALS) [216,217], Facioscapulohumeral dystrophy (FSHD) [218,219], or Limb girdle muscular dystrophy (LGMD) [220], indicating that all these pathologies result in unleashing FAP differentiation. Fibrogenic differentiation of FAPs appears to be mainly controlled by the fibrosis inducer TGFβ. Indeed, appearance of fibrosis in DMD coincides with enhanced TGFβ signaling [221,222], and is exacerbated by genetic variants in the TGFβ regulator Latent TGFβ-binding protein 4 (LTBP4) [223,224]. This effect involves the promotion of FAP differentiation by TGFβ into myofibroblasts, leading to enhanced ECM gene expression [195,225]. Macrophages represent a large source of TGFβ [202]. TGFβ-driven promotion of FAP differentiation was indeed demonstrated to contribute to disease onset and severity in DMD models carrying pathogenic LTBP4 variants [226], and evidence for enhanced TGFβ signaling also exists in mouse models of ALS or FSHD [217,218]. Thus, a key question is to understand whether poor muscle regeneration in pathological context results from the loss of the pro-regenerative functions of FAPs (or their capacity to cross-talk with inflammatory cells), or whether it is a secondary effect of fibrosis and/or fat deposition. The excess deposition of ECM matrix associated with fibrosis is also accompanied with increased presence of proteins involved in ECM assembly, such as small leucine-rich repeat proteoglycans (SLRPs) [139–141], or ECM-modifying enzymes such as Lox [227], which have the potential to compromise myogenic regeneration in muscular dystrophy.

The relative contribution of fibrogenic versus adipogenic differentiation varies between pathologies, with some contexts such as DMD exhibiting a clear pro-fibrotic pattern [195,228], whereas other dystrophies are associated with prominent fat infiltrates [220]. Thus, additional deregulated signals are likely to contribute to the balance between adipogenic and fibrotic differentiation. While the pro-fibrotic TGFβ inhibits adipogenic differentiation of FAPs [225], adipogenic conversion is stimulated by glucocorticoid signaling [229] and by hedgehog signaling [212]. Vice versa, Notch signaling was shown to inhibit adipogenic differentiation [230]. It was reported that nitric oxide inhibits adipogenic differentiation of FAPs, moreover treating mdx mice with a NO-generating drug reduced adipose infiltration via downregulation of *Pparg* expression [231]. Il15 promotes proliferation of FAPs while repressing adipogenic differentiation [232]. Adipogenic differentiation of FAPs also appears to be epigenetically controlled, as HDAC inhibition decreased adipogenesis in vitro and in a DMD mouse model (*Mdx* mice) [215]. Interestingly, HDAC inhibition also induces myogenic gene expression in FAPs, a change that was blunted in aging *Mdx* mice [215,233]. This indicates that the prolonged exposure of FAPs to a context of chronic inflammation and regeneration induces an epigenetically encoded change in FAP biology. Moreover, FAPs are a main source for follistatin, an inhibitor of myostatin. Myostatin induces muscle fiber atrophy, thus follistatin may be involved in maintaining muscle mass. Intriguingly, the beneficial effects of HDAC inhibitors in muscular dystrophy are in part mediated by expression of the BMP inhibitor follistatin from FAPs [215]. Another key study impressively demonstrated that FAP dysfunction in pathological conditions could be detrimental for muscle integrity by demonstrating that, after muscle denervation or in a mouse model for ALS, FAPs secrete increased levels of Il6, which in turn exacerbates muscle atrophy [216].

Of note the differentiation potential of FAPs is not strictly limited to

fibrotic and adipogenic fates. Forced stimulation with exogenous bone morphogenetic protein (BMP), which results in heterotopic ossification of muscle demonstrated osteo-chondrogenic potential [234]. Moreover, FAPs appear to be the source of heterotopic ossification in mouse models of the human genetic condition fibrodysplasia ossificans progressiva (FOP) [235,236]. This is in line with the overall cell surface antigen composition of FAPs resembling mesenchymal stem / progenitor cells that typically show trilineage (fibrogenic, adipogenic, osteo-chondrogenic) potential [190,194]. Even in DMD context, enhanced FAP differentiation can lead to calcification within muscles [226]. This also suggests that FAPs represent a muscle-specific variety of mesenchymal stromal cells as found in many other organs. Furthermore, within this muscle-specific variety, there appears to be a certain degree of molecular heterogeneity the distinguish various subtypes of FAPs, with the profile and distribution of FAP subtypes differing between healthy homeostatic muscles, in healthy muscle after injury, or in pathologic context such as muscle of Mdx mice [228]. This raises the possibility that in addition to changes in the biological properties of FAPs in pathological contexts, each of them might also lead to a differential expansion of FAP subtypes with distinct properties, leading to e.g. predominant expansion of pro-fibrotic FAPs in pathological contexts associated with more fibrosis.

4. Conclusive remarks

While intrinsic mechanisms of myogenic differentiation have been revealed down to great detail, our understanding of the extrinsic regulation of myogenic progenitors in the limb is only at the beginning. We propose three significant gaps in knowledge that future research should address: (1) How are global 3D signaling systems in the limb bud translated into local territories of mesenchyme that express specific transcription factors or combinations of transcription factors? (2) How do locally graded fine-tuned domains of combinatory transcription factor expression translate into an instructive microenvironment towards myogenic cells? (3) What are the components, ECM as well as signaling factors, physically shaping this local bio-mechanical microenvironment? The interplay of myogenic cells and accessory cells, especially mesenchymal progenitors, in regeneration appears in part to parallel developmental events. Therefore, understanding extrinsic regulation of developmental myogenesis may be highly instructive for understanding cellular interplay in regeneration. Often, muscle development and regeneration are addressed separately, however both fields can strongly profit from each other.

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References

[1] J. Capdevila, J.C. Izpisua Belmonte, Patterning mechanisms controlling vertebrate limb development, Annu. Rev. Cell Dev. Biol. 17 (2001) 87–132.
[2] J. Chal, O. Pourquie, Making muscle: skeletal myogenesis *in vivo* and in vitro, Development 144 (12) (2017) 2104–2122.
[3] G. Comai, S. Tajbakhsh, Molecular and cellular regulation of skeletal myogenesis, Curr. Top. Dev. Biol. 110 (2014) 1–73.
[4] S. Nassari, D. Duprez, C. Fournier-Thibault, Non-myogenic contribution to muscle development and homeostasis: the role of connective tissues, Front. Cell Dev. Biol. 5 (2017) 22.
[5] M. Deries, S. Thorsteinsdottir, Axial and limb muscle development: dialogue with the neighbourhood, Cell. Mol. Life Sci. (2016).
[6] E.M. Sefton, G. Kardon, Connecting muscle development, birth defects, and evolution: an essential role for muscle connective tissue, Curr. Top. Dev. Biol. 132 (2019) 137–176.
[7] M. Kieny, A. Mauger, A. Chevallier, M.P. Pautou, Origin and development of avian skeletal musculature, Reprod. Nutr. Dev. 28 (3B) (1988) 673–686.
[8] B. Christ, C.P. Ordahl, Early stages of chick somite development, Anat Embryol (Berl) 191 (5) (1995) 381–396.
[9] A. Chevallier, M. Kieny, A. Mauger, Limb-somite relationship: origin of the limb musculature, J. Embryol. Exp. Morphol. 41 (1977) 245–258.
[10] T. Braun, M. Gautel, Transcriptional mechanisms regulating skeletal muscle differentiation, growth and homeostasis, Nature reviews, Mol. Cell Biol. 12 (6) (2011) 349–361.
[11] B. Kablar, K. Krastel, C. Ying, A. Asakura, S.J. Tapscott, M.A. Rudnicki, MyoD and Myf-5 differentially regulate the development of limb versus trunk skeletal muscle, Development 124 (23) (1997) 4729–4738.
[12] M.A. Rudnicki, T. Braun, S. Hinuma, R. Jaenisch, Inactivation of MyoD in mice leads to up-regulation of the myogenic HLH gene Myf-5 and results in apparently normal muscle development, Cell 71 (3) (1992) 383–390.
[13] M. Buckingham, F. Relaix, PAX3 and PAX7 as upstream regulators of myogenesis, Semin. Cell Dev. Biol. 44 (2015) 115–125.
[14] F. Relaix, D. Rocancourt, A. Mansouri, M. Buckingham, A Pax3/Pax7-dependent population of skeletal muscle progenitor cells, Nature 435 (7044) (2005) 948–953.
[15] J. Gros, M. Manceau, V. Thome, C. Marcelle, A common somitic origin for embryonic muscle progenitors and satellite cells, Nature 435 (7044) (2005) 954–958.
[16] L. Kassar-Duchossoy, E. Giacone, B. Gayraud-Morel, A. Jory, D. Gomes, S. Tajbakhsh, Pax3/Pax7 mark a novel population of primitive myogenic cells during development, Genes Dev. 19 (12) (2005) 1426–1431.
[17] C.A. Picard, C. Marcelle, Two distinct muscle progenitor populations coexist throughout amniote development, Dev. Biol. 373 (1) (2013) 141–148.
[18] L. Bajard, F. Relaix, M. Lagha, D. Rocancourt, P. Daubas, M.E. Buckingham, A novel genetic hierarchy functions during hypaxial myogenesis: Pax3 directly activates Myf5 in muscle progenitor cells in the limb, Genes Dev. 20 (17) (2006) 2450–2464.
[19] J.A. Epstein, P. Lam, L. Jepeal, R.L. Maas, D.N. Shapiro, Pax3 inhibits myogenic differentiation of cultured myoblast cells, J. Biol. Chem. 270 (20) (1995) 11719–11722.
[20] H.C. Olguin, B.B. Olwin, Pax-7 up-regulation inhibits myogenesis and cell cycle progression in satellite cells: a potential mechanism for self-renewal, Dev. Biol. (Basel) 275 (2) (2004) 375–388.
[21] H.C. Olguin, Z. Yang, S.J. Tapscott, B.B. Olwin, Reciprocal inhibition between Pax7 and muscle regulatory factors modulates myogenic cell fate determination, J. Cell Biol. 177 (5) (2007) 769–779.
[22] N. Nandkishore, B. Vyas, A. Javali, S. Ghosh, R. Sambasivan, Divergent early mesoderm specification underlies distinct head and trunk muscle programmes in vertebrates, Development 145 (18) (2018).
[23] K. Bismuth, F. Relaix, Genetic regulation of skeletal muscle development, Exp. Cell Res. 316 (18) (2011) 3081–3086.
[24] R. Grifone, J. Demignon, C. Houbron, E. Souil, C. Niro, M.J. Seller, G. Hamard, P. Maire, Six1 and Six4 homeoproteins are required for Pax3 and Mrf expression during myogenesis in the mouse embryo, Development 132 (9) (2005) 2235–2249.
[25] S. Yokoyama, Y. Ito, H. Ueno-Kudoh, H. Shimizu, K. Uchibe, S. Albini, K. Mitsuoka, S. Miyaki, M. Kiso, A. Nagai, T. Hikata, T. Osada, N. Fukuda, S. Yamashita, D. Harada, V. Mezzano, M. Kasai, P.L. Puri, Y. Hayashizaki, H. Okado, M. Hashimoto, H. Asahara, A systems approach reveals that the myogenesis genome network is regulated by the transcriptional repressor RP58, Dev. Cell 17 (6) (2009) 836–848.
[26] F. Lescroart, W. Hamou, A. Francou, M. Theveniau-Ruissy, R.G. Kelly, M. Buckingham, Clonal analysis reveals a common origin between nonsomite-derived neck muscles and heart myocardium, Proc. Nat. Acad. Sci. U. S. A. 112 (5) (2015) 1446–1451.
[27] F. Lescroart, R.G. Kelly, J.F. Le Garrec, J.F. Nicolas, S.M. Meilhac, M. Buckingham, Clonal analysis reveals common lineage relationships between head muscles and second heart field derivatives in the mouse embryo, Development 137 (19) (2010) 3269–3279.
[28] I. Harel, Y. Maezawa, R. Avraham, A. Rinon, H.Y. Ma, J.W. Cross, N. Leviatan, J. Hegesh, A. Roy, J. Jacob-Hirsch, G. Rechavi, J. Carvajal, S. Tole, C. Kioussi, S. Quaggin, E. Tzahor, Pharyngeal mesoderm regulatory network controls cardiac and head muscle morphogenesis, Proc. Nat. Acad. Sci. U. S. A. 109 (46) (2012) 18839–18844.
[29] R. Sambasivan, B. Gayraud-Morel, G. Dumas, C. Cimper, S. Paisant, R.G. Kelly, S. Tajbakhsh, Distinct regulatory cascades govern extraocular and pharyngeal arch muscle progenitor cell fates, Dev. Cell 16 (6) (2009) 810–821.
[30] A.L. Zacharias, M. Lewandoski, M.A. Rudnicki, P.J. Gage, Pitx2 is an upstream activator of extraocular myogenesis and survival, Dev. Biol. 349 (2) (2011) 395–405.
[31] M. Buckingham, L. Bajard, T. Chang, P. Daubas, J. Hadchouel, S. Meilhac, D. Montarras, D. Rocancourt, F. Relaix, The formation of skeletal muscle: from somite to limb, J. Anat. 202 (1) (2003) 59–68.
[32] K.R. Wotton, F.R. Schubert, S. Dietrich, Hypaxial muscle: controversial classification and controversial data? Results Probl. Cell Differ. 56 (2015) 25–48.
[33] P. Tremblay, S. Dietrich, M. Mericskay, F.R. Schubert, Z. Li, D. Paulin, A crucial

role for Pax3 in the development of the hypaxial musculature and the long-range migration of muscle precursors, Dev. Biol. 203 (1) (1998) 49–61.
[34] J.A. Epstein, D.N. Shapiro, J. Cheng, P.Y. Lam, R.L. Maas, Pax3 modulates expression of the c-Met receptor during limb muscle development, Proc. Nat. Acad. Sci. U. S. A. 93 (9) (1996) 4213–4218.
[35] S. Dietrich, F. Abou-Rebyeh, H. Brohmann, F. Bladt, E. Sonnenberg-Riethmacher, T. Yamaai, A. Lumsden, B. Brand-Saberi, C. Birchmeier, The role of SF/HGF and c-Met in the development of skeletal muscle, Development 126 (8) (1999) 1621–1629.
[36] F. Maina, F. Casagranda, E. Audero, A. Simeone, P.M. Comoglio, R. Klein, C. Ponzetto, Uncoupling of Grb2 from the Met receptor *in vivo* reveals complex roles in muscle development, Cell 87 (3) (1996) 531–542.
[37] C. Schmidt, F. Bladt, S. Goedecke, V. Brinkmann, W. Zschiesche, M. Sharpe, E. Gherardi, C. Birchmeier, Scatter factor/hepatocyte growth factor is essential for liver development, Nature 373 (6516) (1995) 699–702.
[38] F. Bladt, D. Riethmacher, S. Isenmann, A. Aguzzi, C. Birchmeier, Essential role for the c-met receptor in the migration of myogenic precursor cells into the limb bud, Nature 376 (6543) (1995) 768–771.
[39] H. Nord, N. Dennhag, H. Tydinger, J. von Hofsten, The zebrafish HGF receptor met controls migration of myogenic progenitor cells in appendicular development, PLoS One 14 (7) (2019) e0219259.
[40] L. Haines, C. Neyt, P. Gautier, D.G. Keenan, R.J. Bryson-Richardson, G.E. Hollway, N.J. Cole, P.D. Currie, Met and Hgf signaling controls hypaxial muscle and lateral line development in the zebrafish, Development 131 (19) (2004) 4857–4869.
[41] N. Adachi, J. Pascual-Anaya, T. Hirai, S. Higuchi, S. Kuroda, S. Kuratani, Stepwise participation of HGF/MET signaling in the development of migratory muscle precursors during vertebrate evolution, Zool. Lett. 4 (2018) 18.
[42] M. Sachs, H. Brohmann, D. Zechner, T. Muller, J. Hulsken, I. Walther, U. Schaeper, C. Birchmeier, W. Birchmeier, Essential role of Gab1 for signaling by the c-Met receptor *in vivo*, J. Cell Biol. 150 (6) (2000) 1375–1384.
[43] N. Caruso, B. Herberth, F. Lamballe, V. Arce-Gorvel, F. Maina, F. Helmbacher, Plasticity versus specificity in RTK signalling modalities for distinct biological outcomes in motor neurons, BMC Biol. 12 (2014) 56.
[44] C. Prunotto, T. Crepaldi, P.E. Forni, A. Ieraci, R.G. Kelly, S. Tajbakhsh, M. Buckingham, C. Ponzetto, Analysis of Mlc-lacZ Met mutants highlights the essential function of Met for migratory precursors of hypaxial muscles and reveals a role for Met in the development of hyoid arch-derived facial muscles, Dev. Dyn. 231 (3) (2004) 582–591.
[45] F. Maina, G. Pante, F. Helmbacher, R. Andres, A. Porthin, A.M. Davies, C. Ponzetto, R. Klein, Coupling Met to specific pathways results in distinct developmental outcomes, Mol. Cell 7 (6) (2001) 1293–1306.
[46] H. Brohmann, K. Jagla, C. Birchmeier, The role of Lbx1 in migration of muscle precursor cells, Development 127 (2) (2000) 437–445.
[47] E. Vasyutina, J. Stebler, B. Brand-Saberi, S. Schulz, E. Raz, C. Birchmeier, CXCR4 and Gab1 cooperate to control the development of migrating muscle progenitor cells, Genes Dev. 19 (18) (2005) 2187–2198.
[48] M. Masyuk, A. Abduelmula, G. Morosan-Puopolo, V. Odemis, R. Rehimi, N. Khalida, F. Yusuf, J. Engele, H. Tamamura, C. Theiss, B. Brand-Saberi, Retrograde migration of pectoral girdle muscle precursors depends on CXCR4/SDF-1 signaling, Histochem. Cell Biol. 142 (5) (2014) 473–488.
[49] Y. Fan, S. Richelme, E. Avazeri, S. Audebert, F. Helmbacher, R. Dono, F. Maina, Tissue-specific gain of RTK signalling uncovers selective cell vulnerability during embryogenesis, PLoS Genet. 11 (9) (2015) e1005533.
[50] W. Masselink, M. Masaki, D. Sieiro, C. Marcelle, P.D. Currie, Phosphorylation of Lbx1 controls lateral myoblast migration into the limb, Dev. Biol. 430 (2) (2017) 302–309.
[51] L. Besse, C.J. Sheeba, M. Holt, M. Labuhn, S. Wilde, E. Feneck, D. Bell, A. Kucharska, M.P.O. Logan, Individual limb muscle bundles are formed through progressive steps orchestrated by adjacent connective tissue cells during primary myogenesis, Cell Rep. 30 (10) (2020) 3552–3565 e6.
[52] M.E. Swartz, J. Eberhart, E.B. Pasquale, C.E. Krull, EphA4/ephrin-A5 interactions in muscle precursor cell migration in the avian forelimb, Development 128 (23) (2001) 4669–4680.
[53] S. Tozer, M.A. Bonnin, F. Relaix, S. Di Savino, P. Garcia-Villalba, P. Coumailleau, D. Duprez, Involvement of vessels and PDGFB in muscle splitting during chick limb development, Development 134 (14) (2007) 2579–2591.
[54] N. Caruso, B. Herberth, M. Bartoli, F. Puppo, J. Dumonceaux, A. Zimmermann, S. Denadai, M. Lebosse, S. Roche, L. Geng, F. Magdinier, S. Attarian, R. Bernard, F. Maina, N. Levy, F. Helmbacher, Deregulation of the protocadherin gene FAT1 alters muscle shapes: implications for the pathogenesis of facioscapulohumeral dystrophy, PLoS Genet. 9 (6) (2013) e1003550.
[55] F. Helmbacher, Tissue-specific activities of the Fat1 cadherin cooperate to control neuromuscular morphogenesis, PLoS Biol. 16 (5) (2018) e2004734.
[56] P. Mourikis, R. Sambasivan, D. Castel, P. Rocheteau, V. Bizzarro, S. Tajbakhsh, A critical requirement for notch signaling in maintenance of the quiescent skeletal muscle stem cell state, Stem Cells 30 (2) (2012) 243–252.
[57] J. Esteves de Lima, M.A. Bonnin, C. Birchmeier, D. Duprez, Muscle contraction is required to maintain the pool of muscle progenitors via YAP and NOTCH during fetal myogenesis, Elife 5 (2016).
[58] M. Fischer, P. Rikeit, P. Knaus, C. Coirault, YAP-mediated mechanotransduction in skeletal muscle, Front. Physiol. 7 (2016) 41.
[59] A. Zalc, S. Hayashi, F. Aurade, D. Brohl, T. Chang, D. Mademtzoglou, P. Mourikis, Z. Yao, Y. Cao, C. Birchmeier, F. Relaix, Antagonistic regulation of p57kip2 by Hes/Hey downstream of Notch signaling and muscle regulatory factors regulates skeletal muscle growth arrest, Development 141 (14) (2014) 2780–2790.
[60] S. Yennek, M. Burute, M. Thery, S. Tajbakhsh, Cell adhesion geometry regulates non-random DNA segregation and asymmetric cell fates in mouse skeletal muscle stem cells, Cell Rep. 7 (4) (2014) 961–970.
[61] H. Wackerhage, D.P. Del Re, R.N. Judson, M. Sudol, J. Sadoshima, The Hippo signal transduction network in skeletal and cardiac muscle, Sci. Signal. 7 (337) (2014) re4.
[62] J. Lewis, Notch signalling and the control of cell fate choices in vertebrates, Semin. Cell Dev. Biol. 9 (6) (1998) 583–589.
[63] A.B. Chitnis, The role of Notch in lateral inhibition and cell fate specification, Mol. Cell. Neurosci. 6 (4) (1995) 311–321.
[64] S. Agrawal, C. Archer, D.V. Schaffer, Computational models of the Notch network elucidate mechanisms of context-dependent signaling, PLoS Comput. Biol. 5 (5) (2009) e1000390.
[65] M. Sjoqvist, E.R. Andersson, Do as I say, not(ch) as I do: lateral control of cell fate, Dev. Biol. 447 (1) (2019) 58–70.
[66] E. Vasyutina, D.C. Lenhard, C. Birchmeier, Notch function in myogenesis, Cell Cycle 6 (12) (2007) 1451–1454.
[67] A. Louvi, S. Artavanis-Tsakonas, Notch signalling in vertebrate neural development, Nat. Rev. Neurosci. 7 (2) (2006) 93–102.
[68] E. Vasyutina, D.C. Lenhard, H. Wende, B. Erdmann, J.A. Epstein, C. Birchmeier, RBP-J (Rbpsuh) is essential to maintain muscle progenitor cells and to generate satellite cells, Proc. Nat. Acad. Sci. U. S. A. 104 (11) (2007) 4443–4448.
[69] M.C. Delfini, E. Hirsinger, O. Pourquie, D. Duprez, Delta 1-activated notch inhibits muscle differentiation without affecting Myf5 and Pax3 expression in chick limb myogenesis, Development 127 (23) (2000) 5213–5224.
[70] Y. Wen, P. Bi, W. Liu, A. Asakura, C. Keller, S. Kuang, Constitutive Notch activation upregulates Pax7 and promotes the self-renewal of skeletal muscle satellite cells, Mol. Cell. Biol. 32 (12) (2012) 2300–2311.
[71] C.R. Bjornson, T.H. Cheung, L. Liu, P.V. Tripathi, K.M. Steeper, T.A. Rando, Notch signaling is necessary to maintain quiescence in adult muscle stem cells, Stem Cells 30 (2) (2012) 232–242.
[72] K. Schuster-Gossler, R. Cordes, A. Gossler, Premature myogenic differentiation and depletion of progenitor cells cause severe muscle hypotrophy in Delta1 mutants, Proc. Nat. Acad. Sci. U. S. A. 104 (2) (2007) 537–542.
[73] A.C. Rios, O. Serralbo, D. Salgado, C. Marcelle, Neural crest regulates myogenesis through the transient activation of NOTCH, Nature 473 (7348) (2011) 532–535.
[74] A. Mayeuf-Louchart, M. Lagha, A. Danckaert, D. Rocancourt, F. Relaix, S.D. Vincent, M. Buckingham, Notch regulation of myogenic versus endothelial fates of cells that migrate from the somite to the limb, Proc. Nat. Acad. Sci. U. S. A. 111 (24) (2014) 8844–8849.
[75] A. Totaro, T. Panciera, S. Piccolo, YAP/TAZ upstream signals and downstream responses, Nat. Cell Biol. 20 (8) (2018) 888–899.
[76] B. Zhao, X. Wei, W. Li, R.S. Udan, Q. Yang, J. Kim, J. Xie, T. Ikenoue, J. Yu, L. Li, P. Zheng, K. Ye, A. Chinnaiyan, G. Halder, Z.C. Lai, K.L. Guan, Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control, Genes Dev. 21 (21) (2007) 2747–2761.
[77] B. Zhao, X. Ye, J. Yu, L. Li, W. Li, S. Li, J.D. Lin, C.Y. Wang, A.M. Chinnaiyan, Z.C. Lai, K.L. Guan, TEAD mediates YAP-dependent gene induction and growth control, Genes Dev. 22 (14) (2008) 1962–1971.
[78] R.N. Judson, A.M. Tremblay, P. Knopp, R.B. White, R. Urcia, C. De Bari, P.S. Zammit, F.D. Camargo, H. Wackerhage, The Hippo pathway member Yap plays a key role in influencing fate decisions in muscle satellite cells, J. Cell. Sci. 125 (Pt 24) (2012) 6009–6019.
[79] K.I. Watt, R. Judson, P. Medlow, K. Reid, T.B. Kurth, J.G. Burniston, A. Ratkevicius, C. De Bari, H. Wackerhage, Yap is a novel regulator of C2C12 myogenesis, Biochem. Biophys. Res. Commun. 393 (4) (2010) 619–624.
[80] Y. Liu-Chittenden, B. Huang, J.S. Shim, Q. Chen, S.J. Lee, R.A. Anders, J.O. Liu, D. Pan, Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP, Genes Dev. 26 (12) (2012) 1300–1305.
[81] N. Figeac, A.D. Mohamed, C. Sun, M. Schonfelder, D. Matallanas, A. Garcia-Munoz, E. Missiaglia, E. Collie-Duguid, V. De Mello, A.V. Pobbati, J. Pruller, O. Jaka, S.D.R. Harridge, W. Hong, J. Shipley, N. Vargesson, P.S. Zammit, H. Wackerhage, VGLL3 operates via TEAD1, TEAD3 and TEAD4 to influence myogenesis in skeletal muscle, J. Cell. Sci. 132 (13) (2019).
[82] R. Ribas, N. Moncaut, C. Siligan, K. Taylor, J.W. Cross, P.W. Rigby, J.J. Carvajal, Members of the TEAD family of transcription factors regulate the expression of Myf5 in ventral somitic compartments, Dev. Biol. 355 (2) (2011) 372–380.
[83] S. Gunther, M. Mielcarek, M. Kruger, T. Braun, VITO-1 is an essential cofactor of TEF1-dependent muscle-specific gene regulation, Nucl. Acids Res. 32 (2) (2004) 791–802.
[84] M. Honda, K. Hidaka, S.I. Fukada, R. Sugawa, M. Shirai, M. Ikawa, T. Morisaki, Vestigial-like 2 contributes to normal muscle fiber type distribution in mice, Sci. Rep. 7 (1) (2017) 7168.
[85] M. Honda, H. Tsuchimochi, K. Hitachi, S. Ohno, Transcriptional cofactor Vgll2 is required for functional adaptations of skeletal muscle induced by chronic overload, J. Cell. Physiol. 234 (9) (2019) 15809–15824.
[86] A.V. Pobbati, S.W. Chan, I. Lee, H. Song, W. Hong, Structural and functional similarity between the Vgll1-TEAD and the YAP-TEAD complexes, Structure 20 (7) (2012) 1135–1140.
[87] B. Zhao, L. Li, Q. Lu, L.H. Wang, C.Y. Liu, Q. Lei, K.L. Guan, Angiomotin is a novel Hippo pathway component that inhibits YAP oncoprotein, Genes Dev. 25 (1) (2011) 51–63.
[88] C.V. Ragni, N. Diguet, J.F. Le Garrec, M. Novotova, T.P. Resende, S. Pop, N. Charon, L. Guillemot, L. Kitasato, C. Badouel, A. Dufour, J.C. Olivo-Marin, A. Trouve, H. McNeill, S.M. Meilhac, Amotl1 mediates sequestration of the Hippo effector Yap1 downstream of Fat4 to restrict heart growth, Nat. Commun. 8 (2017) 14582.

[89] W. Hong, Angiomotin'g YAP into the nucleus for cell proliferation and cancer development, Sci. Signal. 6 (291) (2013) pe27.
[90] C. Yi, Z. Shen, A. Stemmer-Rachamimov, N. Dawany, S. Troutman, L.C. Showe, Q. Liu, A. Shimono, M. Sudol, L. Holmgren, B.Z. Stanger, J.L. Kissil, The p130 isoform of angiomotin is required for Yap-mediated hepatic epithelial cell proliferation and tumorigenesis, Sci. Signal. 6 (291) (2013) ra77.
[91] S. Dupont, L. Morsut, M. Aragona, E. Enzo, S. Giulitti, M. Cordenonsi, F. Zanconato, J. Le Digabel, M. Forcato, S. Bicciato, N. Elvassore, S. Piccolo, Role of YAP/TAZ in mechanotransduction, Nature 474 (7350) (2011) 179–183.
[92] K. Wada, K. Itoga, T. Okano, S. Yonemura, H. Sasaki, Hippo pathway regulation by cell morphology and stress fibers, Development 138 (18) (2011) 3907–3914.
[93] C.P. Ordahl, N.M. Le Douarin, Two myogenic lineages within the developing somite, Development 114 (2) (1992) 339–353.
[94] C. Lance-Jones, The effect of somite manipulation on the development of motoneuron projection patterns in the embryonic chick hindlimb, Dev. Biol. 126 (2) (1988) 408–419.
[95] A. Chevallier, M. Kieny, On the role of the connective tissue in the patterning of the chick limb musculature, Roux. Arch. Dev. Biol. 191 (1982) 277–280.
[96] G. Kardon, J.K. Campbell, C.J. Tabin, Local extrinsic signals determine muscle and endothelial cell fate and patterning in the vertebrate limb, Dev. Cell 3 (4) (2002) 533–545.
[97] G.B. Shellswell, A.J. Bailey, V.C. Duance, D.J. Restall, Has collagen a role in muscle pattern formation in the developing chick wing? An immunofluorescence study, J. Embryol. Exp. Morphol. 60 (1980) 245–254.
[98] J.L. Durland, M. Sferlazzo, M. Logan, A.C. Burke, Visualizing the lateral somitic frontier in the Prx1Cre transgenic mouse, J. Anat. 212 (5) (2008) 590–602.
[99] M. Logan, J.F. Martin, A. Nagy, C. Lobe, E.N. Olson, C.J. Tabin, Expression of Cre Recombinase in the developing mouse limb bud driven by a Prxl enhancer, Genesis 33 (2) (2002) 77–80.
[100] R.D. Riddle, R.L. Johnson, E. Laufer, C. Tabin, Sonic hedgehog mediates the polarizing activity of the ZPA, Cell 75 (7) (1993) 1401–1416.
[101] R.D. Riddle, M. Ensini, C. Nelson, T. Tsuchida, T.M. Jessell, C. Tabin, Induction of the LIM homeobox gene Lmx1 by WNT7a establishes dorsoventral pattern in the vertebrate limb, Cell 83 (4) (1995) 631–640.
[102] M. Lewandoski, X. Sun, G.R. Martin, Fgf8 signalling from the AER is essential for normal limb development, Nat. Genet. 26 (4) (2000) 460–463.
[103] N.C. Butterfield, E. McGlinn, C. Wicking, The molecular regulation of vertebrate limb patterning, Curr. Top. Dev. Biol. 90 (2010) 319–341.
[104] R. Zeller, J. Lopez-Rios, A. Zuniga, Vertebrate limb bud development: moving towards integrative analysis of organogenesis, Nat. Rev. Genet. 10 (12) (2009) 845–858.
[105] A. Zuniga, Next generation limb development and evolution: old questions, new perspectives, Development 142 (22) (2015) 3810–3820.
[106] D. Duprez, F. Lapointe, F. Edom-Vovard, K. Kostakopoulou, L. Robson, Sonic hedgehog (SHH) specifies muscle pattern at tissue and cellular chick level, in the chick limb bud, Mech. Dev. 82 (1-2) (1999) 151–163.
[107] A.G. Borycki, B. Brunk, S. Tajbakhsh, M. Buckingham, C. Chiang, C.P. Emerson Jr., Sonic hedgehog controls epaxial muscle determination through Myf5 activation, Development 126 (18) (1999) 4053–4063.
[108] D. Duprez, C. Fournier-Thibault, N. Le Douarin, Sonic Hedgehog induces proliferation of committed skeletal muscle cells in the chick limb, Development 125 (3) (1998) 495–505.
[109] M. Kruger, D. Mennerich, S. Fees, R. Schafer, S. Mundlos, T. Braun, Sonic hedgehog is a survival factor for hypaxial muscles during mouse development, Development 128 (5) (2001) 743–752.
[110] M.K. Gustafsson, H. Pan, D.F. Pinney, Y. Liu, A. Lewandowski, D.J. Epstein, C.P. Emerson Jr., Myf5 is a direct target of long-range Shh signaling and Gli regulation for muscle specification, Genes Dev. 16 (1) (2002) 114–126.
[111] J.K. Hu, E. McGlinn, B.D. Harfe, G. Kardon, C.J. Tabin, Autonomous and non-autonomous roles of Hedgehog signaling in regulating limb muscle formation, Genes Dev. 26 (18) (2012) 2088–2102.
[112] Y. Li, Q. Qiu, S.S. Watson, R. Schweitzer, R.L. Johnson, Uncoupling skeletal and connective tissue patterning: conditional deletion in cartilage progenitors reveals cell-autonomous requirements for Lmx1b in dorsal-ventral limb patterning, Development 137 (7) (2010) 1181–1188.
[113] A.E. Brent, T. Braun, C.J. Tabin, Genetic analysis of interactions between the somitic muscle, cartilage and tendon cell lineages during mouse development, Development 132 (3) (2005) 515–528.
[114] I.T. Swinehart, A.J. Schlientz, C.A. Quintanilla, D.P. Mortlock, D.M. Wellik, Hox11 genes are required for regional patterning and integration of muscle, tendon and bone, Development 140 (22) (2013) 4574–4582.
[115] J. Zakany, D. Duboule, The role of Hox genes during vertebrate limb development, Curr. Opin. Genet. Dev. 17 (4) (2007) 359–366.
[116] A. Rinon, S. Lazar, H. Marshall, S. Buchmann-Moller, A. Neufeld, H. Elhanany-Tamir, M.M. Taketo, L. Sommer, R. Krumlauf, E. Tzahor, Cranial neural crest cells regulate head muscle patterning and differentiation during vertebrate embryogenesis, Development 134 (17) (2007) 3065–3075.
[117] A. Rinon, A. Molchadsky, E. Nathan, G. Yovel, V. Rotter, R. Sarig, E. Tzahor, p53 coordinates cranial neural crest cell growth and epithelial-mesenchymal transition/delamination processes, Development 138 (9) (2011) 1827–1838.
[118] F. Puppo, E. Dionnet, M.C. Gaillard, P. Gaildrat, C. Castro, C. Vovan, K. Bertaux, R. Bernard, S. Attarian, K. Goto, I. Nishino, Y. Hayashi, F. Magdinier, M. Krahn, F. Helmbacher, M. Bartoli, N. Levy, Identification of variants in the 4q35 gene FAT1 in patients with a facioscapulohumeral dystrophy-like phenotype, Hum. Mutat. 36 (4) (2015) 443–453.
[119] V. Mariot, S. Roche, C. Hourde, D. Portilho, S. Sacconi, F. Puppo, S. Duguez, P. Rameau, N. Caruso, A.L. Delezoide, C. Desnuelle, B. Bessieres, S. Collardeau, L. Feasson, T. Maisonobe, F. Magdinier, F. Helmbacher, G. Butler-Browne, V. Mouly, J. Dumonceaux, Correlation between low FAT1 expression and early affected muscle in facioscapulohumeral muscular dystrophy, Ann. Neurol. 78 (3) (2015) 387–400.
[120] L. Vickerman, S. Neufeld, J. Cobb, Shox2 function couples neural, muscular and skeletal development in the proximal forelimb, Dev. Biol. (Basel) 350 (2) (2011) 323–336.
[121] C.J. Sheeba, M.P. Logan, The roles of T-Box genes in vertebrate limb development, Curr. Top. Dev. Biol. 122 (2017) 355–381.
[122] P. Hasson, A. DeLaurier, M. Bennett, E. Grigorieva, L.A. Naiche, V.E. Papaioannou, T.J. Mohun, M.P. Logan, Tbx4 and tbx5 acting in connective tissue are required for limb muscle and tendon patterning, Dev. Cell 18 (1) (2010) 148–156.
[123] C. Minguillon, J.J. Gibson-Brown, M.P. Logan, Tbx4/5 gene duplication and the origin of vertebrate paired appendages, Proc. Nat. Acad. Sci. U. S. A. 106 (51) (2009) 21726–21730.
[124] A. DeLaurier, R. Schweitzer, M. Logan, Pitx1 determines the morphology of muscle, tendon, and bones of the hindlimb, Dev. Biol. 299 (1) (2006) 22–34.
[125] M. Spielmann, F. Brancati, P.M. Krawitz, P.N. Robinson, D.M. Ibrahim, M. Franke, J. Hecht, S. Lohan, K. Dathe, A.M. Nardone, P. Ferrari, A. Landi, L. Wittler, B. Timmermann, D. Chan, U. Mennen, E. Klopocki, S. Mundlos, Homeotic arm-to-leg transformation associated with genomic rearrangements at the PITX1 locus, Am. J. Hum. Genet. 91 (4) (2012) 629–635.
[126] B.K. Kragesteen, M. Spielmann, C. Paliou, V. Heinrich, R. Schopflin, A. Esposito, C. Annunziatella, S. Bianco, A.M. Chiariello, I. Jerkovic, I. Harabula, P. Guckelberger, M. Pechstein, L. Wittler, W.L. Chan, M. Franke, D.G. Lupianez, K. Kraft, B. Timmermann, M. Vingron, A. Visel, M. Nicodemi, S. Mundlos, G. Andrey, Dynamic 3D chromatin architecture contributes to enhancer specificity and limb morphogenesis, Nat. Genet. 50 (10) (2018) 1463–1473.
[127] M.P. Colasanto, S. Eyal, P. Mohassel, M. Bamshad, C.G. Bonnemann, E. Zelzer, A.M. Moon, G. Kardon, Development of a subset of forelimb muscles and their attachment sites requires the ulnar-mammary syndrome gene Tbx3, Dis. Model. Mech. 9 (11) (2016) 1257–1269.
[128] G. Kardon, B.D. Harfe, C.J. Tabin, A Tcf4-positive mesodermal population provides a prepattern for vertebrate limb muscle patterning, Dev. Cell 5 (6) (2003) 937–944.
[129] S.J. Mathew, J.M. Hansen, A.J. Merrell, M.M. Murphy, J.A. Lawson, D.A. Hutcheson, M.S. Hansen, M. Angus-Hill, G. Kardon, Connective tissue fibroblasts and Tcf4 regulate myogenesis, Development 138 (2) (2011) 371–384.
[130] P. Vallecillo-García, M. Orgeur, S. Vom Hofe-Schneider, J. Stumm, V. Kappert, D.M. Ibrahim, S.T. Börno, S. Hayashi, F. Relaix, K. Hildebrandt, G. Sengle, M. Koch, B. Timmermann, G. Marazzi, D.A. Sassoon, D. Duprez, S. Stricker, Odd skipped-related 1 identifies a population of embryonic fibro-adipogenic progenitors regulating myogenesis during limb development, Nat. Commun. 8 (1) (2017).
[131] F. Witte, D. Chan, A.N. Economides, S. Mundlos, S. Stricker, Receptor tyrosine kinase-like orphan receptor 2 (ROR2) and Indian hedgehog regulate digit outgrowth mediated by the phalanx-forming region, Proc. Nat. Acad. Sci. U. S. A. 107 (32) (2010) 14211–14216.
[132] A. Bonafede, T. Kohler, M. Rodriguez-Niedenfuhr, B. Brand-Saberi, BMPs restrict the position of premuscle masses in the limb buds by influencing Tcf4 expression, Dev. Biol. 299 (2) (2006) 330–344.
[133] S. Stricker, N. Brieske, J. Haupt, S. Mundlos, Comparative expression pattern of Odd-skipped related genes Osr1 and Osr2 in chick embryonic development, Gene Expr. Patterns 6 (8) (2006) 826–834.
[134] S. Stricker, S. Mathia, J. Haupt, P. Seemann, J. Meier, S. Mundlos, Odd-skipped related genes regulate differentiation of embryonic limb mesenchyme and bone marrow mesenchymal stromal cells, Stem Cells Dev. 21 (4) (2012) 623–633.
[135] S. Nassari, M. Orgeur, C. Blavet, S. Stricker, C. Fournier-Thibault, D. Duprez, In addition to being a marker formuscle connective tissue, Odd skipped-related 2(OSR2) is expressed in differentiated muscle cellsduring chick development, BioRxiv (2018) preprint server.
[136] M. Orgeur, M. Martens, G. Leonte, S. Nassari, M.A. Bonnin, S.T. Borno, B. Timmermann, J. Hecht, D. Duprez, S. Stricker, Genome-wide strategies identify downstream target genes of chick connective tissue-associated transcription factors, Development 145 (7) (2018).
[137] A.J. Merrell, B.J. Ellis, Z.D. Fox, J.A. Lawson, J.A. Weiss, G. Kardon, Muscle connective tissue controls development of the diaphragm and is a source of congenital diaphragmatic hernias, Nat. Genet. 47 (5) (2015) 496–U96.
[138] S. Chen, D.E. Birk, The regulatory roles of small leucine-rich proteoglycans in extracellular matrix assembly, FEBS J. 280 (10) (2013) 2120–2137.
[139] E. Brandan, C. Cabello-Verrugio, C. Vial, Novel regulatory mechanisms for the proteoglycans decorin and biglycan during muscle formation and muscular dystrophy, Matrix Biol. 27 (8) (2008) 700–708.
[140] R. Fadic, V. Mezzano, K. Alvarez, D. Cabrera, J. Holmgren, E. Brandan, Increase in decorin and biglycan in Duchenne Muscular Dystrophy: role of fibroblasts as cell source of these proteoglycans in the disease, J. Cell. Mol. Med. 10 (3) (2006) 758–769.
[141] R. Droguett, C. Cabello-Verrugio, C. Riquelme, E. Brandan, Extracellular proteoglycans modify TGF-beta bio-availability attenuating its signaling during skeletal muscle differentiation, Matrix Biol. 25 (6) (2006) 332–341.
[142] C. Bonnans, J. Chou, Z. Werb, Remodelling the extracellular matrix in development and disease, Nat. Rev. Mol. Cell Biol. 15 (12) (2014) 786–801.
[143] E.H. Barriga, K. Franze, G. Charras, R. Mayor, Tissue stiffening coordinates morphogenesis by triggering collective cell migration *in vivo*, Nature 554 (7693) (2018) 523–527.
[144] A.M. Handorf, Y. Zhou, M.A. Halanski, W.J. Li, Tissue stiffness dictates

development, homeostasis, and disease progression, Organogenesis 11 (1) (2015) 1–15.
[145] L. Kutchuk, A. Laitala, S. Soueid-Bomgarten, P. Shentzer, A.H. Rosendahl, S. Eilot, M. Grossman, I. Sagi, R. Sormunen, J. Myllyharju, J.M. Maki, P. Hasson, Muscle composition is regulated by a Lox-TGFbeta feedback loop, Development 142 (5) (2015) 983–993.
[146] R. Gabay Yehezkely, S. Zaffryar-Eilot, A. Kaganovsky, N. Fainshtain Malka, R. Aviram, I. Livneh, P. Hasson, Intracellular role for the matrix-modifying enzyme lox in regulating transcription factor subcellular localization and activity in muscle regeneration, Dev. Cell (2020).
[147] R. Aviram, S. Zaffryar-Eilot, D. Hubmacher, H. Grunwald, J.M. Maki, J. Myllyharju, S.S. Apte, P. Hasson, Interactions between lysyl oxidases and ADAMTS proteins suggest a novel crosstalk between two extracellular matrix families, Matrix Biol. 75-76 (2019) 114–125.
[148] O. Kraft-Sheleg, S. Zaffryar-Eilot, O. Genin, W. Yaseen, S. Soueid-Baumgarten, O. Kessler, T. Smolkin, G. Akiri, G. Neufeld, Y. Cinnamon, P. Hasson, Localized LoxL3-Dependent fibronectin oxidation regulates myofiber stretch and integrin-mediated adhesion, Dev. Cell 36 (5) (2016) 550–561.
[149] B.K. Hall, T. Miyake, All for one and one for all: condensations and the initiation of skeletal development, Bioessays 22 (2) (2000) 138–147.
[150] G. Kardon, Muscle and tendon morphogenesis in the avian hind limb, Development 125 (20) (1998) 4019–4032.
[151] A. Vortkamp, K. Lee, B. Lanske, G.V. Segre, H.M. Kronenberg, C.J. Tabin, Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein, Science 273 (5275) (1996) 613–622.
[152] B. St-Jacques, M. Hammerschmidt, A.P. McMahon, Indian hedgehog signaling regulates proliferation and differentiation of chondrocytes and is essential for bone formation, Genes Dev. 13 (16) (1999) 2072–2086.
[153] Y. Bren-Mattison, M. Hausburg, B.B. Olwin, Growth of limb muscle is dependent on skeletal-derived Indian hedgehog, Dev. Biol. (Basel) 356 (2) (2011) 486–495.
[154] A.H. Huang, T.J. Riordan, B. Pryce, J.L. Weibel, S.S. Watson, F. Long, V. Lefebvre, B.D. Harfe, H.S. Stadler, H. Akiyama, S.F. Tufa, D.R. Keene, R. Schweitzer, Musculoskeletal integration at the wrist underlies the modular development of limb tendons, Development 142 (14) (2015) 2431–2441.
[155] F. Edom-Vovard, B. Schuler, M.A. Bonnin, M.A. Teillet, D. Duprez, Fgf4 positively regulates scleraxis and tenascin expression in chick limb tendons, Dev. Biol. 247 (2) (2002) 351–366.
[156] M.A. Bonnin, C. Laclef, R. Blaise, S. Eloy-Trinquet, F. Relaix, P. Maire, D. Duprez, Six1 is not involved in limb tendon development, but is expressed in limb connective tissue under Shh regulation, Mech. Dev. 122 (4) (2005) 573–585.
[157] R. Schweitzer, J.H. Chyung, L.C. Murtaugh, A.E. Brent, V. Rosen, E.N. Olson, A. Lassar, C.J. Tabin, Analysis of the tendon cell fate using Scleraxis, a specific marker for tendons and ligaments, Development 128 (19) (2001) 3855–3866.
[158] L. Gaut, D. Duprez, Tendon development and diseases, Wiley Interdiscip. Rev. Dev. Biol. 5 (1) (2016) 5–23.
[159] H. Wang, F. Noulet, F. Edom-Vovard, S. Tozer, F. Le Grand, D. Duprez, Bmp signaling at the tips of skeletal muscles regulates the number of fetal muscle progenitors and satellite cells during development, Dev. Cell 18 (4) (2010) 643–654.
[160] A.H. Huang, T.J. Riordan, L. Wang, S. Eyal, E. Zelzer, J.V. Brigande, R. Schweitzer, Repositioning forelimb superficialis muscles: tendon attachment and muscle activity enable active relocation of functional myofibers, Dev. Cell 26 (5) (2013) 544–551.
[161] M.G. Hanson, L.T. Landmesser, Characterization of the circuits that generate spontaneous episodes of activity in the early embryonic mouse spinal cord, J. Neurosci. 23 (2) (2003) 587–600.
[162] M.G. Hanson, L.T. Landmesser, Increasing the frequency of spontaneous rhythmic activity disrupts pool-specific axon fasciculation and pathfinding of embryonic spinal motoneurons, J. Neurosci. 26 (49) (2006) 12769–12780.
[163] M.G. Hanson, L.T. Landmesser, Normal patterns of spontaneous activity are required for correct motor axon guidance and the expression of specific guidance molecules, Neuron 43 (5) (2004) 687–701.
[164] M. Weitkunat, A. Kaya-Copur, S.W. Grill, F. Schnorrer, Tension and force-resistant attachment are essential for myofibrillogenesis in Drosophila flight muscle, Curr. Biol. 24 (7) (2014) 705–716.
[165] M. Weitkunat, M. Brasse, A.R. Bausch, F. Schnorrer, Mechanical tension and spontaneous muscle twitching precede the formation of cross-striated muscle *in vivo*, Development 144 (7) (2017) 1261–1272.
[166] S. Nassari, C. Blavet, M.A. Bonnin, S. Stricker, D. Duprez, C. Fournier-Thibault, The chemokines CXCL12 and CXCL14 differentially regulate connective tissue markers during limb development, Sci. Rep. 7 (1) (2017) 17279.
[167] N. Felsenthal, E. Zelzer, Mechanical regulation of musculoskeletal system development, Development 144 (23) (2017) 4271–4283.
[168] H.H. Chen, S. Hippenmeyer, S. Arber, E. Frank, Development of the monosynaptic stretch reflex circuit, Curr. Opin. Neurobiol. 13 (1) (2003) 96–102.
[169] T. Akay, W.G. Tourtellotte, S. Arber, T.M. Jessell, Degradation of mouse locomotor pattern in the absence of proprioceptive sensory feedback, Proc. Nat. Acad. Sci. U. S. A. 111 (47) (2014) 16877–16882.
[170] K. Senzaki, S. Ozaki, M. Yoshikawa, Y. Ito, T. Shiga, Runx3 is required for the specification of TrkC-expressing mechanoreceptive trigeminal ganglion neurons, Mol. Cell. Neurosci. 43 (3) (2010) 296–307.
[171] R. Blecher, S. Krief, T. Galili, I.E. Biton, T. Stern, E. Assaraf, D. Levanon, E. Appel, Y. Anekstein, G. Agar, Y. Groner, E. Zelzer, The proprioceptive system masterminds spinal alignment: insight into the mechanism of scoliosis, Dev. Cell 42 (4) (2017) 388–399 e3.
[172] C.F. Bentzinger, Y.X. Wang, N.A. Dumont, M.A. Rudnicki, Cellular dynamics in the muscle satellite cell niche, EMBO Rep. 14 (12) (2013) 1062–1072.
[173] M.N. Wosczyna, T.A. Rando, A muscle stem cell support group: coordinated cellular responses in muscle regeneration, Dev. Cell 46 (2) (2018) 135–143.
[174] A. Mauro, Satellite cell of skeletal muscle fibers, J. Biophys. Biochem. Cytol. 9 (1961) 493–495.
[175] J. Schienda, K.A. Engleka, S. Jun, M.S. Hansen, J.A. Epstein, C.J. Tabin, L.M. Kunkel, G. Kardon, Somitic origin of limb muscle satellite and side population cells, Proc. Nat. Acad. Sci. U. S. A. 103 (4) (2006) 945–950.
[176] R.B. White, A.S. Bierinx, V.F. Gnocchi, P.S. Zammit, Dynamics of muscle fibre growth during postnatal mouse development, BMC Dev. Biol. 10 (2010) 21.
[177] J.F. Bachman, A. Klose, W.X. Liu, N.D. Paris, R.S. Blanc, M. Schmalz, E. Knapp, J.V. Chakkalakal, Prepubertal skeletal muscle growth requires Pax7-expressing satellite cell-derived myonuclear contribution, Development 145 (20) (2018).
[178] A.C. Keefe, J.A. Lawson, S.D. Flygare, Z.D. Fox, M.P. Colasanto, S.J. Mathew, M. Yandell, G. Kardon, Muscle stem cells contribute to myofibres in sedentary adult mice, Nat. Commun. 6 (2015) 7087.
[179] H. Yin, F. Price, M.A. Rudnicki, Satellite cells and the muscle stem cell niche, Physiol. Rev. 93 (1) (2013) 23–67.
[180] M.B. Baghdadi, D. Castel, L. Machado, S.I. Fukada, D.E. Birk, F. Relaix, S. Tajbakhsh, P. Mourikis, Reciprocal signalling by Notch-Collagen V-CALCR retains muscle stem cells in their niche, Nature 557 (7707) (2018) 714–718.
[181] S. Eliazer, J.M. Muncie, J. Christensen, X. Sun, R.S. D'Urso, V.M. Weaver, A.S. Brack, Wnt4 from the niche controls the mechano-properties and quiescent state of muscle stem cells, Cell Stem Cell 25 (5) (2019) 654–665 e4.
[182] R. Mounier, F. Chretien, B. Chazaud, Blood vessels and the satellite cell niche, Curr. Top. Dev. Biol. 96 (2011) 121–138.
[183] E. Kostallari, Y. Baba-Amer, S. Alonso-Martin, P. Ngoh, F. Relaix, P. Lafuste, R.K. Gherardi, Pericytes in the myovascular niche promote post-natal myofiber growth and satellite cell quiescence, Development 142 (7) (2015) 1242–1253.
[184] R. Abou-Khalil, F. Le Grand, G. Pallafacchina, S. Valable, F.J. Authier, M.A. Rudnicki, R.K. Gherardi, S. Germain, F. Chretien, A. Sotiropoulos, P. Lafuste, D. Montarras, B. Chazaud, Autocrine and paracrine angiopoietin 1/Tie-2 signaling promotes muscle satellite cell self-renewal, Cell Stem Cell 5 (3) (2009) 298–309.
[185] J.G. Tidball, Mechanisms of muscle injury, repair, and regeneration, Compr. Physiol. 1 (4) (2011) 2029–2062.
[186] S. Kuang, K. Kuroda, F. Le Grand, M.A. Rudnicki, Asymmetric self-renewal and commitment of satellite stem cells in muscle, Cell 129 (5) (2007) 999–1010.
[187] C.J. Mann, E. Perdiguero, Y. Kharraz, S. Aguilar, P. Pessina, A.L. Serrano, P. Munoz-Canoves, Aberrant repair and fibrosis development in skeletal muscle, Skelet. Muscle 1 (1) (2011) 21.
[188] A.W. Joe, L. Yi, A. Natarajan, F. Le Grand, L. So, J. Wang, M.A. Rudnicki, F.M. Rossi, Muscle injury activates resident fibro/adipogenic progenitors that facilitate myogenesis, Nat. Cell Biol. 12 (2) (2010) 153–163.
[189] A. Uezumi, S. Fukada, N. Yamamoto, S. Takeda, K. Tsuchida, Mesenchymal progenitors distinct from satellite cells contribute to ectopic fat cell formation in skeletal muscle, Nat. Cell Biol. 12 (2) (2010) 143–152.
[190] A. Uezumi, S. Fukada, N. Yamamoto, M. Ikemoto-Uezumi, M. Nakatani, M. Morita, A. Yamaguchi, H. Yamada, I. Nishino, Y. Hamada, K. Tsuchida, Identification and characterization of PDGFRalpha+ mesenchymal progenitors in human skeletal muscle, Cell Death Dis. 5 (2014) e1186.
[191] K.J. Mitchell, A. Pannerec, B. Cadot, A. Parlakian, V. Besson, E.R. Gomes, G. Marazzi, D.A. Sassoon, Identification and characterization of a non-satellite cell muscle resident progenitor during postnatal development, Nat. Cell Biol. 12 (3) (2010) 257–266.
[192] A. Pannerec, L. Formicola, V. Besson, G. Marazzi, D.A. Sassoon, Defining skeletal muscle resident progenitors and their cell fate potentials, Development 140 (14) (2013) 2879–2891.
[193] M.M. Murphy, J.A. Lawson, S.J. Mathew, D.A. Hutcheson, G. Kardon, Satellite cells, connective tissue fibroblasts and their interactions are crucial for muscle regeneration, Development 138 (17) (2011) 3625–3637.
[194] A. Uezumi, M. Ikemoto-Uezumi, K. Tsuchida, Roles of nonmyogenic mesenchymal progenitors in pathogenesis and regeneration of skeletal muscle, Front. Physiol. 5 (2014) 68.
[195] O. Contreras, F.M. Rossi, E. Brandan, Adherent muscle connective tissue fibroblasts are phenotypically and biochemically equivalent to stromal fibro/adipogenic progenitors, Matrix Biol. Plus 2 (100006) (2019).
[196] R.W. Scott, M. Arostegui, R. Schweitzer, F.M.V. Rossi, T.M. Underhill, Hic1 defines quiescent mesenchymal progenitor subpopulations with distinct functions and fates in skeletal muscle regeneration, Cell Stem Cell 25 (6) (2019) 797–813 e9.
[197] L. Giordani, G.J. He, E. Negroni, H. Sakai, J.Y.C. Law, M.M. Siu, R. Wan, A. Corneau, S. Tajbakhsh, T.H. Cheung, F. Le Grand, High-dimensional single-cell cartography reveals novel skeletal muscle-resident cell populations, Mol. Cell 74 (3) (2019) 609–621 e6.
[198] H. Soliman, B. Paylor, R.W. Scott, D.R. Lemos, C. Chang, M. Arostegui, M. Low, C. Lee, D. Fiore, P. Braghetta, V. Pospichalova, C.E. Barkauskas, V. Korinek, A. Rampazzo, K. MacLeod, T.M. Underhill, F.M.V. Rossi, Pathogenic potential of Hic1-Expressing cardiac stromal progenitors, Cell Stem Cell 26 (2) (2020) 205–220 e8.
[199] J.E. Heredia, L. Mukundan, F.M. Chen, A.A. Mueller, R.C. Deo, R.M. Locksley, T.A. Rando, A. Chawla, Type 2 innate signals stimulate fibro/adipogenic progenitors to facilitate muscle regeneration, Cell 153 (2) (2013) 376–388.
[200] A.A. Mueller, C.T. van Velthoven, K.D. Fukumoto, T.H. Cheung, T.A. Rando, Intronic polyadenylation of PDGFRalpha in resident stem cells attenuates muscle fibrosis, Nature 540 (7632) (2016) 276–279.
[201] D.R. Lemos, F. Babaeijandaghi, M. Low, C.K. Chang, S.T. Lee, D. Fiore, R.H. Zhang, A. Natarajan, S.A. Nedospasov, F.M. Rossi, Nilotinib reduces muscle fibrosis in chronic muscle injury by promoting TNF-mediated apoptosis of fibro/adipogenic

progenitors, Nat. Med. 21 (7) (2015) 786–794.
[202] G. Juban, M. Saclier, H. Yacoub-Youssef, A. Kernou, L. Arnold, C. Boisson, S. Ben Larbi, M. Magnan, S. Cuvellier, M. Theret, B.J. Petrof, I. Desguerre, J. Gondin, R. Mounier, B. Chazaud, AMPK activation regulates LTBP4-Dependent TGF-beta1 secretion by pro-inflammatory macrophages and controls fibrosis in duchenne muscular dystrophy, Cell Rep. 25 (8) (2018) 2163–2176 e6.
[203] Y. Saito, T.S. Chikenji, T. Matsumura, M. Nakano, M. Fujimiya, Exercise enhances skeletal muscle regeneration by promoting senescence in fibro-adipogenic progenitors, Nat. Commun. 11 (1) (2020) 889.
[204] Y. Zhang, H. Li, Z. Lian, N. Li, Myofibroblasts protect myoblasts from intrinsic apoptosis associated with differentiation via beta1 integrin-PI3K/Akt pathway, Dev. Growth Differ. 52 (8) (2010) 725–733.
[205] M.N. Wosczyna, C.T. Konishi, E.E. Perez Carbajal, T.T. Wang, R.A. Walsh, Q. Gan, M.W. Wagner, T.A. Rando, Mesenchymal stromal cells are required for regeneration and homeostatic maintenance of skeletal muscle, Cell Rep. 27 (7) (2019) 2029–2035 e5.
[206] D. Fiore, R.N. Judson, M. Low, S. Lee, E. Zhang, C. Hopkins, P. Xu, A. Lenzi, F.M. Rossi, D.R. Lemos, Pharmacological blockage of fibro/adipogenic progenitor expansion and suppression of regenerative fibrogenesis is associated with impaired skeletal muscle regeneration, Stem Cell Res. 17 (1) (2016) 161–169.
[207] J. Stumm, P. Vallecillo-García, S. Vom Hofe-Schneider, D. Ollitrault, H. Schrewe, A.N. Economides, G. Marazzi, D.A. Sassoon, S. Stricker, Odd skipped-related 1 (Osr1) identifies muscle-interstitial fibro-adipogenic progenitors (FAPs) activated by acute injury, Stem Cell Res. 32 (2018) 8–16.
[208] A. Urciuolo, M. Quarta, V. Morbidoni, F. Gattazzo, S. Molon, P. Grumati, F. Montemurro, F.S. Tedesco, B. Blaauw, G. Cossu, G. Vozzi, T.A. Rando, P. Bonaldo, Collagen VI regulates satellite cell self-renewal and muscle regeneration, Nat. Commun. 4 (2013) 1964.
[209] L. Lukjanenko, S. Karaz, P. Stuelsatz, U. Gurriaran-Rodriguez, J. Michaud, G. Dammone, F. Sizzano, O. Mashinchian, S. Ancel, E. Migliavacca, S. Liot, G. Jacot, S. Metairon, F. Raymond, P. Descombes, A. Palini, B. Chazaud, M.A. Rudnicki, C.F. Bentzinger, J.N. Feige, Aging disrupts muscle stem cell function by impairing matricellular WISP1 secretion from fibro-adipogenic progenitors, Cell Stem Cell 24 (3) (2019) 433–446 e7.
[210] E.W. Roberts, A. Deonarine, J.O. Jones, A.E. Denton, C. Feig, S.K. Lyons, M. Espeli, M. Kraman, B. McKenna, R.J. Wells, Q. Zhao, O.L. Caballero, R. Larder, A.P. Coll, S. O'Rahilly, K.M. Brindle, S.A. Teichmann, D.A. Tuveson, D.T. Fearon, Depletion of stromal cells expressing fibroblast activation protein-alpha from skeletal muscle and bone marrow results in cachexia and anemia, J. Exp. Med. 210 (6) (2013) 1137–1151.
[211] A. Uezumi, T. Ito, D. Morikawa, N. Shimizu, T. Yoneda, M. Segawa, M. Yamaguchi, R. Ogawa, M.M. Matev, Y. Miyagoe-Suzuki, S. Takeda, K. Tsujikawa, K. Tsuchida, H. Yamamoto, S. Fukada, Fibrosis and adipogenesis originate from a common mesenchymal progenitor in skeletal muscle, J. Cell. Sci. 124 (Pt 21) (2011) 3654–3664.
[212] D. Kopinke, E.C. Roberson, J.F. Reiter, Ciliary hedgehog signaling restricts injury-induced adipogenesis, Cell 170 (2) (2017) 340–351 e12.
[213] P. Pessina, Y. Kharraz, M. Jardi, S. Fukada, A.L. Serrano, E. Perdiguero, P. Munoz-Canoves, Fibrogenic cell plasticity blunts tissue regeneration and aggravates muscular dystrophy, Stem Cell Reports 4 (6) (2015) 1046–1060.
[214] O. Contreras, D.L. Rebolledo, J.E. Oyarzun, H.C. Olguin, E. Brandan, Connective tissue cells expressing fibro/adipogenic progenitor markers increase under chronic damage: relevance in fibroblast-myofibroblast differentiation and skeletal muscle fibrosis, Cell Tissue Res. 364 (3) (2016) 647–660.
[215] C. Mozzetta, S. Consalvi, V. Saccone, M. Tierney, A. Diamantini, K.J. Mitchell, G. Marazzi, G. Borsellino, L. Battistini, D. Sassoon, A. Sacco, P.L. Puri, Fibroadipogenic progenitors mediate the ability of HDAC inhibitors to promote regeneration in dystrophic muscles of young, but not old Mdx mice, EMBO Mol. Med. 5 (4) (2013) 626–639.
[216] L. Madaro, M. Passafaro, D. Sala, U. Etxaniz, F. Lugarini, D. Proietti, M.V. Alfonsi, C. Nicoletti, S. Gatto, M. De Bardi, R. Rojas-Garcia, L. Giordani, S. Marinelli, V. Pagliarini, C. Sette, A. Sacco, P.L. Puri, Denervation-activated STAT3-IL-6 signalling in fibro-adipogenic progenitors promotes myofibres atrophy and fibrosis, Nat. Cell Biol. 20 (8) (2018) 917–927.
[217] D. Gonzalez, O. Contreras, D.L. Rebolledo, J.P. Espinoza, B. van Zundert, E. Brandan, ALS skeletal muscle shows enhanced TGF-beta signaling, fibrosis and induction of fibro/adipogenic progenitor markers, PLoS One 12 (5) (2017) e0177649.
[218] D. Bosnakovski, A.S. Shams, C. Yuan, M.T. da Silva, E.T. Ener, C.W. Baumann, A.J. Lindsay, M. Verma, A. Asakura, D.A. Lowe, M. Kyba, Transcriptional and cytopathological hallmarks of FSHD in chronic DUX4-expressing mice, J. Clin. Invest. (2020).
[219] D. Bosnakovski, S.S.K. Chan, O.O. Recht, L.M. Hartweck, C.J. Gustafson, L.L. Athman, D.A. Lowe, M. Kyba, Muscle pathology from stochastic low level DUX4 expression in an FSHD mouse model, Nat. Commun. 8 (1) (2017) 550.
[220] M.W. Hogarth, A. Defour, C. Lazarski, E. Gallardo, J. Diaz Manera, T.A. Partridge, K. Nagaraju, J.K. Jaiswal, Fibroadipogenic progenitors are responsible for muscle loss in limb girdle muscular dystrophy 2B, Nat. Commun. 10 (1) (2019) 2430.
[221] E.M. MacDonald, R.D. Cohn, TGFbeta signaling: its role in fibrosis formation and myopathies, Curr. Opin. Rheumatol. 24 (6) (2012) 628–634.
[222] Y.W. Chen, K. Nagaraju, M. Bakay, O. McIntyre, R. Rawat, R. Shi, E.P. Hoffman, Early onset of inflammation and later involvement of TGFbeta in Duchenne muscular dystrophy, Neurology 65 (6) (2005) 826–834.
[223] K.M. Flanigan, E. Ceco, K.M. Lamar, Y. Kaminoh, D.M. Dunn, J.R. Mendell, W.M. King, A. Pestronk, J.M. Florence, K.D. Mathews, R.S. Finkel, K.J. Swoboda, E. Gappmaier, M.T. Howard, J.W. Day, C. McDonald, E.M. McNally, R.B. Weiss, LTBP4 genotype predicts age of ambulatory loss in Duchenne muscular dystrophy, Ann. Neurol. 73 (4) (2013) 481–488.
[224] A. Heydemann, E. Ceco, J.E. Lim, M. Hadhazy, P. Ryder, J.L. Moran, D.R. Beier, A.A. Palmer, E.M. McNally, Latent TGF-beta-binding protein 4 modifies muscular dystrophy in mice, J. Clin. Invest. 119 (12) (2009) 3703–3712.
[225] O. Contreras, M. Cruz-Soca, M. Theret, H. Soliman, L.W. Tung, E. Groppa, F.M. Rossi, E. Brandan, Cross-talk between TGF-beta and PDGFRalpha signaling pathways regulates the fate of stromal fibro-adipogenic progenitors, J. Cell. Sci. 132 (19) (2019).
[226] D.A. Mazala, J.S. Novak, M.W. Hogarth, M. Nearing, P. Adusumalli, C.B. Tully, N.F. Habib, H. Gordish-Dressman, Y.W. Chen, J.K. Jaiswal, T.A. Partridge, TGF-beta-driven muscle degeneration and failed regeneration underlie disease onset in a DMD mouse model, JCI Insight 5 (6) (2020).
[227] L.R. Smith, D.W. Hammers, H.L. Sweeney, E.R. Barton, Increased collagen cross-linking is a signature of dystrophin-deficient muscle, Muscle Nerve 54 (1) (2016) 71–78.
[228] B. Malecova, S. Gatto, U. Etxaniz, M. Passafaro, A. Cortez, C. Nicoletti, L. Giordani, A. Torcinaro, M. De Bardi, S. Bicciato, F. De Santa, L. Madaro, P.L. Puri, Dynamics of cellular states of fibro-adipogenic progenitors during myogenesis and muscular dystrophy, Nat. Commun. 9 (1) (2018) 3670.
[229] Y. Dong, K.A. Silva, Y. Dong, L. Zhang, Glucocorticoids increase adipocytes in muscle by affecting IL-4 regulated FAP activity, FASEB J. 28 (9) (2014) 4123–4132.
[230] M. Marinkovic, C. Fuoco, F. Sacco, A. Cerquone Perpetuini, G. Giuliani, E. Micarelli, T. Pavlidou, L.L. Petrilli, A. Reggio, F. Riccio, F. Spada, S. Vumbaca, A. Zuccotti, L. Castagnoli, M. Mann, C. Gargioli, G. Cesareni, Fibro-adipogenic progenitors of dystrophic mice are insensitive to NOTCH regulation of adipogenesis, Life Sci. Alliance 2 (3) (2019).
[231] N. Cordani, V. Pisa, L. Pozzi, C. Sciorati, E. Clementi, Nitric oxide controls fat deposition in dystrophic skeletal muscle by regulating fibro-adipogenic precursor differentiation, Stem Cells 32 (4) (2014) 874–885.
[232] X. Kang, M.Y. Yang, Y.X. Shi, M.M. Xie, M. Zhu, X.L. Zheng, C.K. Zhang, Z.L. Ge, X.T. Bian, J.T. Lv, Y.J. Wang, B.H. Zhou, K.L. Tang, Interleukin-15 facilitates muscle regeneration through modulation of fibro/adipogenic progenitors, Cell Commun. Signal 16 (1) (2018) 42.
[233] V. Saccone, S. Consalvi, L. Giordani, C. Mozzetta, I. Barozzi, M. Sandona, T. Ryan, A. Rojas-Munoz, L. Madaro, P. Fasanaro, G. Borsellino, M. De Bardi, G. Frige, A. Termanini, X. Sun, J. Rossant, B.G. Bruneau, M. Mercola, S. Minucci, P.L. Puri, HDAC-regulated myomiRs control BAF60 variant exchange and direct the functional phenotype of fibro-adipogenic progenitors in dystrophic muscles, Genes Dev. 28 (8) (2014) 841–857.
[234] M.N. Wosczyna, A.A. Biswas, C.A. Cogswell, D.J. Goldhamer, Multipotent progenitors resident in the skeletal muscle interstitium exhibit robust BMP-dependent osteogenic activity and mediate heterotopic ossification, J. Bone Miner. Res. 27 (5) (2012) 1004–1017.
[235] J.B. Lees-Shepard, M. Yamamoto, A.A. Biswas, S.J. Stoessel, S.E. Nicholas, C.A. Cogswell, P.M. Devarakonda, M.J. Schneider Jr., S.M. Cummins, N.P. Legendre, S. Yamamoto, V. Kaartinen, J.W. Hunter, D.J. Goldhamer, Activin-dependent signaling in fibro/adipogenic progenitors causes fibrodysplasia ossificans progressiva, Nat. Commun. 9 (1) (2018) 471.
[236] D. Dey, J. Bagarova, S.J. Hatsell, K.A. Armstrong, L. Huang, J. Ermann, A.J. Vonner, Y. Shen, A.H. Mohedas, A. Lee, E.M. Eekhoff, A. van Schie, M.B. Demay, C. Keller, A.J. Wagers, A.N. Economides, P.B. Yu, Two tissue-resident progenitor lineages drive distinct phenotypes of heterotopic ossification, Sci. Transl. Med. 8 (366) (2016) 366ra163.