Cellular and Molecular Life Sciences (2021) 78:5043–5049
https://doi.org/10.1007/s00018-021-03838-2

REVIEW

The relationship between muscle stem cells and motor neurons

Monika Zmojdzian[1] · **Krzysztof Jagla**[1]

Received: 5 January 2021 / Revised: 25 March 2021 / Accepted: 8 April 2021 / Published online: 16 April 2021

Abstract
Neuromuscular system is constituted of multi-fibrillar muscles, tendons, motor neurons and associated muscle stem cells. Stereotyped pattern of muscle innervation and muscle-specific interactions with tendon cells suggest that neuromuscular system develops in a coordinated way. Remarkably, upon regeneration, coordinated assembly of all neuromuscular components is also critical to rebuild functional muscle. Thus, to ensure muscle function, the neuromuscular system components need to interact both during development and regeneration. Over the last decades, interactions between muscles and tendons, muscles and motor neurons and between muscles and muscle stem cells have been extensively analysed and documented. However, only recent evidence indicates that muscle stem cells interact with motor neurons and that these interactions contribute to building functional muscle both during development and regeneration. From this perspective, we discuss here the relationship between muscle stem cells and motor neurons during *Drosophila* neuromuscular system development and adverse impact of affected muscle stem cell–motor neuron interactions in regenerating vertebrate muscle.

Keywords Muscle stem cell · AMP · Satellite cell · Motor neuron · Drosophila

AMPs, the muscle stem cells of the fruit fly

During *Drosophila* development, two waves of myogenesis take place, each of which leading to the generation of fully functional neuromuscular systems. The first, embryonic wave leads to the formation of larval body wall muscles that ensure crawling behaviour; while, the second wave takes place during metamorphosis to generate, in addition to adult body wall muscles, the flight and leg muscles necessary for the locomotion of the adult fly. Both larval and adult fly muscles develop specific myotendinous and neuromuscular junctions (MTJ and NMJ) that ensure their connection to tendons and motor neurons. Furthermore, the specified during the first myogenic wave muscle stem cells (MuSCs) called adult muscle precursors (AMPs) [1] also contribute to coordinated development of the larval neuromuscular system. AMPs are generated during mid-embryogenesis from the subset of muscle progenitors cells that undergo asymmetric cell division giving rise to AMPs and to muscle founder cells (FCs) [2, 3]. In each abdominal hemisegment, six AMPs are specified (Fig. 1a). They are located at stereotyped positions and tightly associated with set of neighbouring muscles. AMPs send out numerous short filopodia enabling their contact with muscles [4] and long cellular processes aligning with the PNS nerves [5]. While the FCs enter the myogenic differentiation process, the AMPs stay quiescent and undifferentiated during the embryonic and first part of the larval life. They get then reactivated at mid larval stage [2, 4] to generate pool of the myoblasts, which will then build the adult muscles. In parallel, they also generate a restricted population of adult MuSCs, which were recently found associated with the multi-fibrillar flight muscles of the adult fly [6, 7]. All these properties make the *Drosophila* AMPs similar to vertebrate MuSCs.

Identity and diversity of the AMPs

The muscle founder cells, which support the identity of the future muscles, fuse with surrounding fusion competent myoblasts, and serve as seeds for individual muscles in the embryo. Each FC is characterised not only by the expression of muscle differentiation factor Mef2 but also by a combinatorial code of identity factors (iTFs) that determine

✉ Krzysztof Jagla
christophe.jagla@uca.fr

[1] GReD Institute-INSERM U1103, CNRS UMR6293, Université Clermont Auvergne, 28, place Henri-Dunant, 63000 Clermont-Ferrand, France

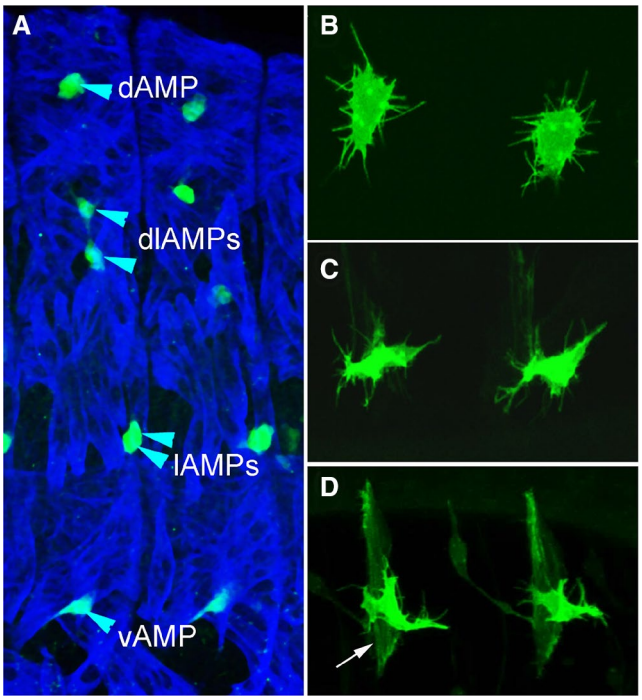

Fig. 1 Spatial positioning and shapes of AMPs, the *Drosophila* muscle stem cells. **a** M6-GFP AMP sensor, as previously shown by Figeac et al. [5] detects six AMPs in each abdominal hemisegment (green). Arrowheads point to one ventral (vAMP), two lateral (lAMPs), two dorso-lateral (dlAMPs) and one dorsal AMP (dAMP). Embryonic body wall muscles are stained with anti-β3-Tubulin (blue). **b**, **c**, **d** AMP shapes in living embryos revealed using cell membrane tagged M6-gapGFP sensor (refer to Aradhya et al. [4]). Notice that newly specified AMPs (**b**) adopt rounded shapes with numerous filopodia and become more elongated in a later embryonic stage (**c**). **d** An in vivo view of lateral AMPs associated with the segment border muscle (SBM). Arrow points to the SBM

individual properties of a muscle it gives rise to [8]. In contrast to FCs, the AMPs express general muscle stem cell markers such as the myogenic b-HLH transcription factor Twist [9] and zinc finger homeobox factor Zfh1 and are characterised by the expression of Notch targets Him and E(spl)m6 (Table 1) [4, 5]. Him and Zfh1 are able to counteract Mef2-driven myogenic differentiation [10, 11]. Notch plays a critical role in the reactivation of dormant AMPs [4] and in the maintenance of adult fly MuSCs stemness [7]. Similarly, in vertebrates, Notch promotes the quiescent MuSCs state [12, 13] and as demonstrated for Notch2 also ensures the progression of MuSCs into reactivated state [14]. Like FCs, the AMPs also express a code of iTFs highlighting their diversity. For example, both the anterior and the posterior lateral AMP express the homeodomain transcription factors Ladybird (Lb), while only the anterior one is Krüppel (Kr) positive (Table 1) [5]. Interestingly, Lb- and Lb/Kr-positive lateral AMPs are located in close vicinity of lateral transverse (LT) Kr-expressing muscles and the Lb-positive segment border muscle (SBM) suggesting that the same iTF code underlies spatial positioning of both embryonic muscles and AMPs. In a similar way, the ventral AMPs expressing Slouch (Slou) and Pox meso (Table 1) [5] lie close to Slou/Pox-meso-positive ventral VA3 and VT1 muscles. The fact that AMPs express specific iTFs could make them competent for the formation of a given type of muscle in the adult fly. Furthermore, it was demonstrated that EGF signalling is required for specification and maintenance of lateral, dorso-lateral and dorsal but not ventral AMPs [5] indicating an additional level of AMPs diversity.

Dormant AMPs associate with peripheral nerves

The AMPs lie dormant during embryonic life and get reactivated at the larval stage. To get insight into cell shape and behaviour of quiescent AMPs, we generated

Table 1 *Drosophila* genes specifically expressed in AMPs, adult *Drosophila* MuSCs and their vertebrate counterparts expressed in vertebrate MuSCs

Drosophila gene	Expression in AMPs	Expression in adult Drosophila MuSCs	Reference	Vertebrate orthologue	Expression in vertebrate MuSCs	Reference
Twi	All AMPs	Not expressed	[5–7]	Twist1, Twist2 Myf5	Subset of MuSCs (Twi2) Activated MuSCs	[31] [20]
Zfh1	All AMPs	All MuSCs short isoform (Zfh1-RA)	[6, 7]	ZEB1	In quiescent MuSCs	[18]
Gsb	Not expressed	Not known		Pax 7	All MuSCs	[19, 20]
Gsb	Not expressed	Not known		Pax 3	Subset of MuSCs	[19, 20]
Notch effector: E(spl)M6	All AMPs	GMR30C06 (Notch-Gal4)	[5, 6]	Notch effectors: Hes1, Hey1, HeyL	In quiescent MuSCs	[12, 13]
Him	All AMPs	Not known	[5, 10]	No orthologue		
Lb	Subset of AMPs	Not known	[5]	Lbx1	Not known	
Slou	Subset of AMPs	Not known	[5]	Nkx1.1	Not known	

the AMP-sensor line expressing a cell membrane-targeted GFP (gap-GFP) [5]. Live imaging experiments showed that directly after specification, AMPs are of rounded shape and send out numerous filopodia (Fig. 1b). Some of the filopodia get in contact with navigating motor neurons and these connections are stabilised promoting an extended AMPs shape (Fig. 1c, Fig. 2). Mechanisms driving AMP cell shape change as well as molecules that ensure their interactions with motor neurons are not yet known. In parallel, AMPs associate with specific set of somatic muscles. For example, the two Lb-positive lateral AMPs (Fig. 1d) get associated with the Lb-expressing SBM. Later in embryonic development, AMPs send long cellular processes, which follow the main neural branches of the peripheral nervous system (PNS) (Fig. 2). This allows quiescent AMPs to form network of interconnected cells, while their cellular bodies are extended on cognate muscles. Consistent with these observations, we found that AMPs contact with muscles and PNS ensure their proper spatial positioning whereas interconnections between AMPs play a role in the maintenance of elongated AMPs shape.

AMPs attract motor neurons and ensure proper innervation of embryonic muscles

As stated before, embryonic AMPs contact specific set of muscles, which behave as their niche and use nerves as support for long protrusions. Interestingly, AMPs are also located in the path of navigating intersegmental (ISN) and segmental a (SNa) motor neuron branches (Fig. 2). Our recent data [1] show that navigating ISN contacts first the dorso-lateral AMPs and then dorsal AMPs to target specific set of muscles (Fig. 2a). This suggests guiding role of dorso-lateral and dorsal AMPs in defining ISN trajectory. Indeed, when dorsal AMP positioning is affected, the ISN trajectory shifts to meet the displaced AMP. However, loss of dorso-lateral and dorsal AMPs does not prevent ISN-dependent muscle innervation. In contrast, loss of lateral AMPs impedes innervation of the SBM muscle by the navigating SNa. In fact, in normal development, the SNa is sub-divided into dorsal and lateral branch innervating the lateral transvers muscles (LTs) and segmental border muscle (SBM), respectively. Lateral branch defasciculates from SNa in the close vicinity of lateral AMPs, before innervating the SBM. In vivo experiments showed an active filopodia

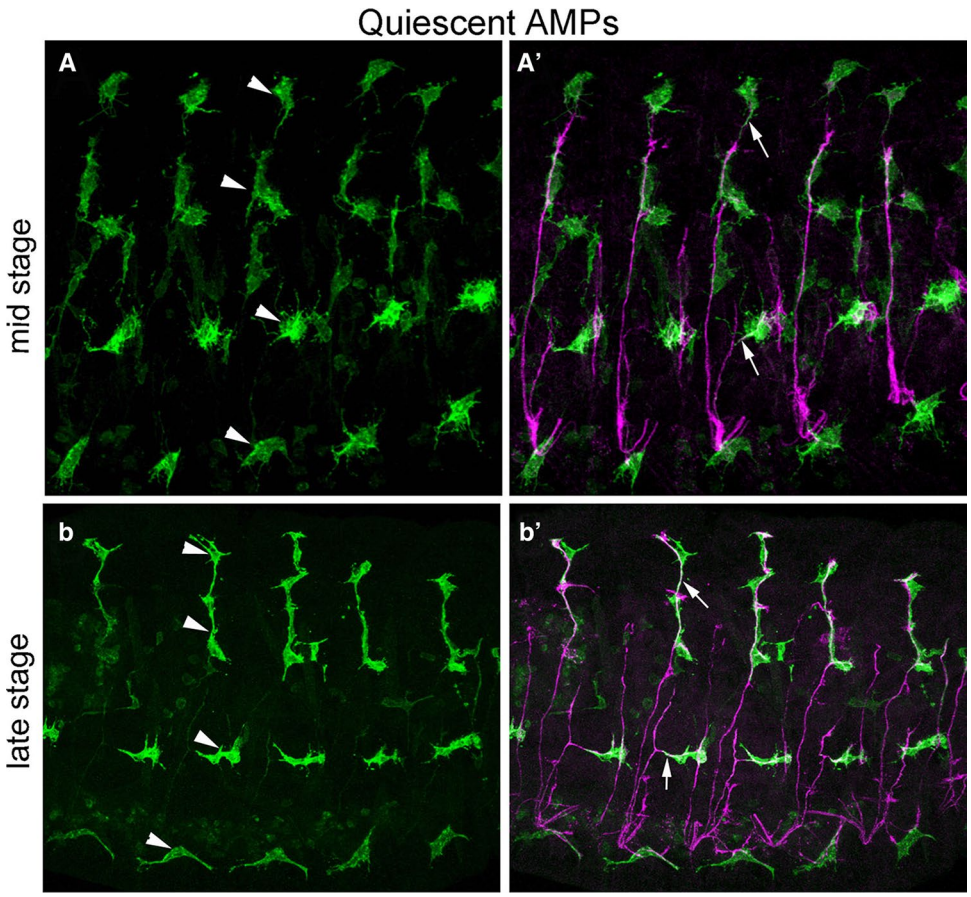

Fig. 2 Quiescent AMPs are in the path of navigating motor neurons. Lateral views of five hemisegments of mid stage (A, A') and late stage (B, B') M6-gapGFP *Drosophila* embryos stained for GFP to reveal AMPs (green, arrowheads) and their cellular extensions (arrows) and for Fasciclin 2 (purple) to detect motor neurons (refer to Lavergne et al. [1]). Notice that in the mid-stage embryos, dorsal AMPs send cellular protrusions ventrally to interact with the navigating ISN nerve (arrow in A') and are in the path of the ISN in the later embryonic stage (arrow in B'). Similarly, lateral AMPs send filopodia and start to interact with SNa (arrow in A') in mid-stage embryos. This interaction triggers defasciculation of the lateral SNa branch (arrow in B'), which innervates SBM muscle

dynamic of lateral AMPs, which extend filopodia toward the SNa enabling defasciculation of the lateral branch (Fig. 2b). Consistently, loss of lateral AMPs cells leads to the absence of lateral branch indicating instructive role of lateral AMPs in fasciculation and proper innervation of SBM muscle. How the quiescent AMPs guide navigating motor axons and contribute to proper muscle innervation remain unknown, but the AMP-specific expression of sidestep, one of the cell adhesion molecules involved in muscle innervation, makes it a potential player [1].

Motor neurons ensure survival of reactivated AMPs

At the beginning of larval life, the AMPs are still interconnected by long cellular processes. Shortly after this network is lost, however, individual AMPs keep contact with the neighbouring muscles [4] and with motor neurons. To stay in their niche, AMPs adopt extended shapes along the larval muscles and in contact with innervating them motor neurons (Fig. 3a). This observation prompted us to test whether the association of AMPs with muscles and motor neurons could play a role in driving AMPs exit from the dormant state [4]. It was shown that AMPs require nutrient-dependent switch in metabolism and need muscle niche-derived inductive molecules to enter proliferation. Induction of Insulin/TOR pathway in AMPs or forced secretion of *Drosophila* Insulin-like peptide from the muscle (dIlp6) but not from the neural cells positively regulated AMPs reactivation. Interestingly, the increased Notch and dMyc activities also induced the reactivation of AMPs. The activation of Notch in dividing symmetrically AMPs was found to be ligand independent and involving accumulation of Deltex (Table 1) [4, 15]. Thus, AMPs get reactivated via the muscle niche-induced Insulin/Notch/Myc cascade. Furthermore, genetic epistasis experiments revealed that Notch acts downstream of Insulin pathway and dMyc functions downstream of Notch promoting AMPs exit from the quiescent state [4, 12]. One remaining question is the role of persisting AMPs association with the motor neurons (Fig. 3b). It has been previously suggested that the motor axons could serve as templates for migration of proliferating AMPs [16]. Our recent data show that motor neurons ensure not only AMPs distribution but also their maintenance [1]. Indeed, genetic ablation of SNa leads to the loss of anterior lateral AMPs normally associated with the SNa; while, the posterior lateral AMPs aligned on the transverse nerve (TN) stay unaffected [1]. Altogether, these results point to a crosstalk between AMPs and motor neurons, with the quiescent AMPs attracting navigating motor axons, which hereafter ensure survival of activated AMPs in the larval stages.

Activated AMPs give rise to adult *Drosophila* muscles and MuSCs

At the beginning of pupa stage, the majority of generated during embryogenesis muscles undergo tissue histolysis and get replaced by the adult musculature. Adult muscles originate from the activated AMPs, which differentiate into adult FCs and fusion competent myoblasts [17]. Depending

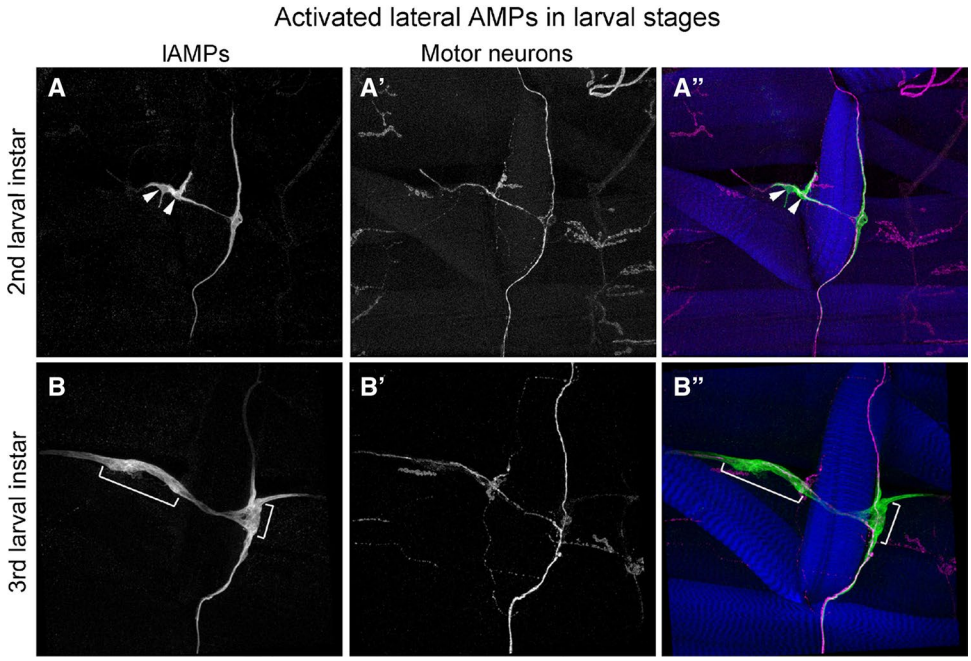

Fig. 3 Activated AMPs keep associated with motor neurons (refer to Lavergne et al. [1]). All views show lateral AMPs, which in larval stages are subdivided into two subpopulations one lying anteriorly and one posteriorly (green in A",B",C") to the SBM muscle (blue in A",B"). The anterior lAMPs (arrowheads in A) are associated with lateral branch of SNa, while the posterior lAMPs align on the transverse nerve (TN). Notice that reactivation of AMPs takes place in 2nd larval instar (arrowheads in A and A" point to two lAMPs, issue of the first division) and leads to generation of two pools of activated AMPs in 3rd instar (brackets in B and B") which remain aligned on SNa and TN nerves

on their dorsal–ventral and anterior–posterior position in the embryo, the AMPs will build specific adult fly muscles. For example, the anterior, thoracic AMPs associated with imaginal discs give rise to adult flight and leg muscles; whereas, abdominal AMPs are at the origin of the adult body wall muscles. Activated abdominal AMPs are distributed along the peripheral nerves (Fig. 3b), which as we demonstrated are required for their maintenance [1]. Interestingly, like during the first embryonic myogenic wave, some of the adult muscle progenitors do not follow differentiation programme and become adult *Drosophila* MuSCs. They stay quiescent under the basal lamina of the myofibers but in the response to the muscle injury undergo Notch-activated proliferation and fuse with the damaged muscle fibres [6, 7], thus sharing anatomical and functional features with vertebrate MuSCs, the satellite cells. In contrast to embryonic and larval AMPs, the adult fly MuSCs do not express Twi but can be identified by the persistent expression of *Zfh1*, an ortholog of vertebrate satellite cell marker *ZEB* [18] known to counteract myogenic differentiation [11]. Genetic analysis revealed the existence of two different *Zfh1* isoforms, *Zfh1-long* and an alternate *Zfh1-short* [7], whose respective levels appear to control the balance between AMPs stemness and differentiation. In contrast to the short, the long *Zfh1* isoform contains the seed for *miR-8*, whose action decreases Zfh1 protein level. The activated AMPs mainly expressing the *Zfh1-long* and exposed to *miR-8* progressively lose Zfh1 protein and enter differentiation whereas a subset of AMPs with a Notch-induced expression of *Zfh1-short* sustain Zfh1, escape differentiation and become adult fly MuSCs [7]. Developed by Boukhatmi and Bray GFP sensor (Enh3-GFP) allows to recognise the arising from the activated AMPs adult MuSCs [7]. However, whether motor neurons that trigger AMPs maintenance are also instructive to adult *Drosophila* MuSCs remains to be investigated.

Vertebrate MuSCs and their interactions with motor neurons

Vertebrate MuSCs also called the satellite cells ensure skeletal muscle growth, maintenance and regeneration. In a quiescent state, they are tightly associated with muscle fibres and located beneath the basal lamina in a specialised niche. When activated upon stress such as muscle injury, satellite cells generate the pool of myogenic progenitors, which get committed, differentiate and repair damaged myofibers. Importantly, activated MuSCs are also able to self-renew via asymmetric cell divisions, which allow to restore the quiescent satellite cell pool. Large body of evidence [19, 20] including recent single-cell RNAseq analyses [21–23] show that satellite cells (like *Drosophila* AMPs) are heterogenous both in terms of markers they express and their behaviour. All satellite cells express Pax7; however, only a subset of them co-express Pax7 and Pax3. MuSCs expressing high levels of Pax7 exhibit slow division rate; whereas those with a low Pax7 expression divide fast and are committed to differentiation [24]. The activated satellite cells are also positive for myogenic regulatory factor Myf5, and could arise from Myf5-positive cells or via asymmetric division from Myf5-negative quiescent satellite cells. Thus, the activated satellite cells differ from those residing within their niche; however, whether different muscle types associate with particular subsets of MuSCs remains an open question. Below we discuss observations suggesting that the vertebrate satellite cells not only repair muscles by fusing with damaged fibres but also, like their *Drosophila* counterparts, interact with motor neurons and play a role in proper innervation of regenerating muscle. The muscle–nerve connections allow executing voluntary muscle functions and when they do not form properly or are severed, muscles degenerate. This occurs in pathological states of neuromuscular diseases, and also happens to some extent in healthy individuals during ageing. Liu et al. [25] by tracking satellite cells in mice after severing muscle–nerve connections, observed that the satellite cells accumulated around the regenerating neuromuscular junctions and that in satellite cell deficient mice muscle–nerve connections were severely affected after healing. Thus, this work provided experimental evidence for the role of vertebrate MuSCs in neuromuscular junction regeneration in response to denervation and it was further supported by finding that satellite cell depletion was sufficient to induce neuromuscular junction degeneration in young mice [26]. Consistent with their key role, recent study [27] demonstrated that after muscle denervation, satellite cells keep all their stem cell features. The relationships between satellite cells and motor neurons also appear to underlie the pathomechanisms of spinal muscular atrophy (SMA), a frequent recessive autosomal neuromuscular disorder characterised by degeneration of motor neurons associated with muscle atrophy. Mutations in the survival of motor neuron gene (*SMN1*) encoding ubiquitously expressed protein involved in assembly of spliceosomal RNPs are responsible for SMA [28] However, whether SMA phenotype is primarily due to *SMN* loss in motor neurons, muscles or satellite cells remains a subject of discussion. Nicole et al. [29] observed that *SMN* reduction in satellite cells has a critical impact on the severity of SMA. Reduced SMN levels in satellite cells were sufficient to worsen SMA phenotype leading to the loss of satellite cells, decrease in the number of regenerating fibres and early mutant mice lethality. Thus it is reasonable to suggest that loss of SMN in satellite cells promotes motor neuron survival and muscle innervation by Liu et al., [25, 26] negative effect of satellite cell depletion on muscle innervation it is reasonable to suggest that loss of *SMN* in satellite cells promotes motor neuron survival and muscle

innervation. Indeed, in co-cultures of SMA satellite cells with myofibres and motor neurons, myofiber innervation was affected with motor neurons undergoing apoptosis prior innervation; whereas in co-cultures involving control satellite cells, innervation of myofibers by motor neurons took place normally [30]. Overall, these data point to the role of satellite cells in proper muscle re-innervation after injury. Whether vertebrate MuSCs play a similar role during muscle development remains an open question.

Conclusion

Muscle stem cells represent an integral component of neuromuscular system ensuring muscle growth, regeneration and homeostasis. Growing body of evidence suggests that MuSCs actively interact with their cellular environment including the innervating muscles motor neurons. The role and molecular mechanisms underlying these interactions only begin to be investigated. We focused here on the *Drosophila* model, and on observations that reveal impact of quiescent MuSCs on the innervation of developing muscles and on the association of activated MuSCs with motor neurons, which in turn ensure MuSCs maintenance. Because MuSCs are also required for efficient re-innervation of regenerating vertebrate muscles, we conclude that interactions between muscle stem cells and motor neurons play a conserved role in the formation of functional muscle.

Acknowledgements This work was funded by strategic grant of AFM-Telethon to MyoNeurAlp aliance (MZ and KJ) and by the iSITE CAP20-25 grant to MZ.

Author contributions KJ conceptualised the manuscript, MZ and KJ wrote the manuscript.

Funding This work was supported by the iSITE CAP20-25 grant and the strategic AFM-Téléthon grant to MyoNeurAlp consortium.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Lavergne G, Zmojdzian M, Da Ponte JP et al (2020) Drosophila adult muscle precursor cells contribute to motor axon pathfinding and proper innervation of embryonic muscles. Development 147(4):183004
2. Ruiz Gómez M, Bate M (1997) Segregation of myogenic lineages in Drosophila requires numb. Development 124:4857–4866
3. Figeac N, Daczewska M, Marcelle C, Jagla K (2007) Muscle stem cells and model systems for their investigation. Dev Dyn 236:3332–3342
4. Aradhya R, Zmojdzian M, Da Ponte JP, Jagla K (2015) Muscle niche-driven Insulin-Notch-Myc cascade reactivates dormant Adult Muscle Precursors in Drosophila. Elife 4:e08497
5. Figeac N, Jagla T, Aradhya R et al (2010) Drosophila adult muscle precursors form a network of interconnected cells and are specified by the rhomboid-triggered EGF pathway. Development 137:1965–1973
6. Chaturvedi D, Reichert H, Gunage RD, VijayRaghavan K (2017) Identification and functional characterization of muscle satellite cells in Drosophila. Elife 6:e30107
7. Boukhatmi H, Bray S (2018) A population of adult satellite-like cells in Drosophila is maintained through a switch in RNA-isoforms. Elife 7:e35954
8. Tixier V, Bataillé L, Jagla K (2010) Diversification of muscle types: Recent insights from Drosophila. Exp Cell Res 316:3019–3027
9. Bate M, Rushton E, Currie DA (1991) Cells with persistent twist expression are the embryonic precursors of adult muscles in Drosophila. Development 113:79–89
10. Liotta D, Han J, Elgar S et al (2007) The Him gene reveals a balance of inputs controlling muscle differentiation in Drosophila. Curr Biol 17:1409–1413
11. Postigo AA, Ward E, Skeath JB, Dean DC (1999) zfh-1, the Drosophila homologue of ZEB, is a transcriptional repressor that regulates somatic myogenesis. Mol Cell Biol 19:7255–7263
12. Mourikis P, Sambasivan R, Castel D et al (2012) A critical requirement for notch signaling in maintenance of the quiescent skeletal muscle stem cell state. Stem Cells 3:243–252
13. Noguchi YT, Nakamura M, Hino N et al (2019) Cell-autonomous and redundant roles of Hey1 and HeyL in muscle stem cells: HeyL requires Hes1 to bind diverse DNA sites. Development. https://doi.org/10.1242/dev.163618
14. Fujimaki S, Seko D, Kitajima Y et al (2018) Notch1 and Notch2 coordinately regulate stem cell function in the quiescent and activated states of muscle satellite cells. Stem Cells 36:278–285
15. Aradhya R, Jagla K (2020) Insulin-dependent non-canonical activation of notch in Drosophila: A story of notch-induced muscle stem cell proliferation. Adv Exp Med Biol 1227:131–144
16. Farrell ER, Keshishian H (1999) Laser ablation of persistent twist cells in Drosophila: muscle precursor fate is not segmentally restricted. Development 126:273–280
17. Dutta D, Shaw S, Maqbool T et al (2005) Drosophila Heartless acts with Heartbroken/Dof in muscle founder differentiation. PLoS Biol 3:e337
18. Siles L, Ninfali C, Cortés M et al (2019) ZEB1 protects skeletal muscle from damage and is required for its regeneration. Nat Commun 10:1364
19. Buckingham M, Relaix F (2007) The role of Pax genes in the development of tissues and organs: Pax3 and Pax7 regulate muscle progenitor cell functions. Annu Rev Cell Dev Biol 23:645–673
20. Feige P, Brun CE, Ritso M, Rudnicki MA (2018) Orienting muscle stem cells for regeneration in homeostasis, aging, and disease. Cell Stem Cell 23:653–664
21. De Micheli AJ, Laurilliard EJ, Heinke CL et al (2020) Single-cell analysis of the muscle stem cell hierarchy identifies heterotypic communication signals involved in skeletal muscle regeneration. Cell Rep 30:3583-3595.e5
22. Dos Santos M, Backer S, Saintpierre B et al (2020) Single-nucleus RNA-seq and FISH identify coordinated transcriptional activity in mammalian myofibers. Nat Commun 11:5102
23. Petrany MJ, Swoboda CO, Sun C et al (2020) Single-nucleus RNA-seq identifies transcriptional heterogeneity in multinucleated skeletal myofibers. Nat Commun 11:6374
24. Rocheteau P, Gayraud-Morel B, Siegl-Cachedenier I et al (2012) A subpopulation of adult skeletal muscle stem cells retains all template DNA strands after cell division. Cell 148:112–125

25. Liu W, Wei-LaPierre L, Klose A et al (2015) Inducible depletion of adult skeletal muscle stem cells impairs the regeneration of neuromuscular junctions. Elife 4:e09221
26. Liu W, Klose A, Forman S et al (2017) Loss of adult skeletal muscle stem cells drives age-related neuromuscular junction degeneration. Elife 6:e26464
27. Wong A, Garcia SM, Tamaki S et al (2021) Satellite cell activation and retention of muscle regenerative potential after long-term denervation. Stem Cells 39:331–344
28. Frugier T, Nicole S, Cifuentes-Diaz C, Melki J (2002) The molecular bases of spinal muscular atrophy. Curr Opin Genet Dev 12:294–298
29. Nicole S, Desforges B, Millet G et al (2003) Intact satellite cells lead to remarkable protection against Smn gene defect in differentiated skeletal muscle. J Cell Biol 161:571–582
30. Guettier-Sigrist S, Hugel B, Coupin G et al (2002) Possible pathogenic role of muscle cell dysfunction in motor neuron death in spinal muscular atrophy. Muscle Nerve 25:700–708
31. Liu N, Glynnis A, Garry A et al (2017) Twist2-dependent progenitor cell contributes to adult skeletal muscle. Nat Cell Biol 19:202–213