Published in final edited form as:
Adv Exp Med Biol. 2019 January 01; 1147: 319–344. doi:10.1007/978-3-030-16908-4_15.

Pericytes in muscular dystrophies

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Abstract

The muscular dystrophies are a heterogeneous group of inherited myopathies characterised by the progressive wasting of skeletal muscle tissue. Pericytes have been shown to make muscle in vitro and to contribute to skeletal muscle regeneration in several animal models, although recent data has shown this to be controversial. In fact, some pericyte subpopulations have been shown to contribute to fibrosis and adipose deposition in muscle. In this chapter we explore the identity and the multifaceted role of pericytes in dystrophic muscle, potential therapeutic applications and the current need to overcome the hurdles of characterisation (both to identify pericyte subpopulations and track cell fate), to prevent deleterious differentiation towards myogenic-inhibiting subpopulations, and to improve cell proliferation and engraftment efficacy.

Keywords

pericytes; muscular dystrophy; muscle; stem cells; cell therapy; muscle regeneration; adipogenesis; chondrogenesis; fibrosis; plasticity

1 Skeletal Muscle and Muscular dystrophies

Skeletal muscle is the most abundant tissue in humans and its main roles are to generate movement, support soft tissues, maintain posture, and contribute to energy metabolism and temperature control (Frontera and Ochala, 2015). It is characterised by a well-defined structure of connective tissues and muscle fibres (or myofibres), which are multinucleated, post-mitotic syncytial cells containing contractile units named sarcomeres. During skeletal muscle histogenesis, muscle fibres are generated by the fusion of paired-box transcription factor 3- (Pax3) and Pax7-expressing mesodermal progenitors (Bentzinger et al., 2012; Buckingham, 2006; Comai and Tajbakhsh, 2014). After birth, they grow in size thanks to the fusion of satellite cells (Yablonka-Reuveni, 2011; Yin et al., 2013), a population of muscle stem cells located between the plasma membrane of myofibres (sarcolemma) and the basal lamina, that are responsible for growth, repair, and regeneration of adult skeletal muscle

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(Mauro, 1961; Relaix and Zammit, 2012). Satellite cells are quiescent in physiological conditions but can be activated after muscle injury or by specific signalling pathways (Dumont et al., 2015; Relaix and Zammit, 2012; Verdijk et al., 2014; Yin et al., 2013). Once activated, they proliferate and the majority of them differentiate along the myogenic programme in order to replace damaged muscle fibres. Alternatively, they undergo self-renewal to replenish the stem cell pool (Rocheteau et al., 2012; Zammit et al., 2004). Satellite cells are characterised by the expression of Pax7, which is SC-specific marker in skeletal muscle. Many also express caveolin-1, integrin-α7, M-cadherin, CD56/NCAM, CD29/integrin-β1 and syndecans 3 and 4, although differences in expression patterns are observed between species, location and activation stage [reviewed in detail in (Boldrin et al., 2010; Tedesco et al., 2010; Tedesco et al., 2017; Yin et al., 2013)]. Satellite cells and their derived myoblast progeny are considered the main muscle stem cells, required for complete myogenic regeneration [reviewed in (Relaix and Zammit, 2012; Zammit et al., 2006)]. In the last two decades, several muscle and non-muscle stem/progenitor cells with variable myogenic potencies have been isolated. For comprehensive reviews on the topic please refer to (Negroni et al., 2016; Tedesco et al., 2010; Tedesco et al., 2017).

Muscular dystrophies are a clinically and genetically heterogeneous group of rare neuromuscular genetic disorders sharing common pathological features (Mercuri and Muntoni, 2013). Despite their heterogeneity in muscle wasting distribution, disease severity, inheritance, age of onset and progression rate, they are characterised by repeated cycles of skeletal muscle degeneration/regeneration, changes in myofibre size and inflammation, which ultimately results in progressive muscle wasting. In the most severe forms, muscle weakness leads to early loss of ambulation and to a premature death by cardiorespiratory failure (Manzur and Muntoni, 2009; Mercuri and Muntoni, 2013). Many muscular dystrophies are caused by mutations in genes coding for proteins that belong to the dystrophin-associated glycoprotein complex (DAGC) (Ervasti and Campbell, 1991). The DAGC is a multiprotein complex located at the muscle fibre membrane (sarcolemma) and provides a strong mechanical link between intracellular cytoskeleton and the extracellular matrix; it plays a pivotal role in stabilising the sarcolemma and in maintaining myofiber integrity during muscle contraction (Emery, 2002; Straub and Campbell, 1997). As a consequence, mutations disrupting the DAGC result in increased sarcolemma fragility and contraction induced-fibre damage, which in turn lead to repeated cycles of myofibre degeneration/regeneration and ultimately to the replacement of the skeletal muscle tissue with fibrotic and adipose tissues (Matsumura and Campbell, 1994; Michalak and Opas, 1997; Straub and Campbell, 1997; Worton, 1995). Other muscular dystrophies can be caused by mutations in ubiquitously expressed proteins that result in muscle pathologies, such as mutations of nuclear envelope components. Recently, nextgeneration sequencing is helping to identify new genes responsible for previously undefined muscular dystrophies (Carss et al., 2013; Hara et al., 2011; Mitsuhashi and Kang, 2012).

The most common are Duchenne (DMD), Becker (BMD) and limb-girdle (LGMD). DMD is caused by mutations in the X-linked gene that codifies for dystrophin, a rod-shaped cytoplasmic protein belonging to the DAGC (Ervasti and Campbell, 1991; Michalak and Opas, 1997; Straub et al., 1992). DMD has an early onset and a severe disease progression. Becker MD (BMD) is the milder allelic variant of DMD, which has a slower progression

and later onset. LGMDs represent one of the most heterogeneous groups, which are further subclassified according to the genetic defect responsible for the individual forms and inheritance (Emery, 2002; Mercuri and Muntoni, 2013).

Although muscular dystrophies are often fatal diseases for which no cure currently exists, many therapeutic strategies are being developed and tested in basic, pre-clinical and clinical studies [reviewed in (Benedetti et al., 2013; Bengtsson et al., 2016; Lin and Wang, 2018; Negroni et al., 2016; Pini et al., 2017; Scoto et al., 2018)].

2 Skeletal Muscle Pericytes

2a Pericyte ontogeny

Pericytes are an heterogeneous population of contractile mural cells that surround and support blood vessels in all vascularised tissues (Hirschi and D'Amore, 1996). They were thought to be exclusively associated with the microvasculature, but evidence supports their presence also on higher order vessels (Campagnolo et al., 2010), except the lymphatic vessels (Norrmen et al., 2011). Pericytes can be defined and distinguished from other perivascular cells, such as smooth muscle cells, by a combination of criteria including anatomical location, morphology and gene/protein expression pattern (Armulik et al., 2011). Notably, pericytes can be distinguished from other endothelial-associated perivascular cells by their location embedded within the vascular basement membrane (Sims, 1986).

Despite pericytes being observed and described for the first time more than a century ago (Eberth, 1871; Rouget, 1873; Zimmermann, 1923), fundamental questions about their origin and functions remain partially unanswered. This is mainly due to the struggle in identifying a common pericyte ancestor. Numerous lineage-tracing experiments have shown that during embryogenesis, pericytes from different tissues originate from diverse sources, so that as a result a single vessel may be composed by pericytes of diverse developmental origins (Majesky, 2007; Majesky et al., 2011). Recently, lineage-tracing studies have shown even more diversity, with subsets of pericytes with hematopoietic (Yamazaki et al., 2017) and macrophage (Prazeres et al., 2018) origin.

Interestingly, pericytes in the aorta appear to have multiple developmental sources (Majesky, 2007; Majesky et al., 2011), adding an additional layer of complexity to the pericyte's ontogeny debate (Birbrair et al., 2017; Dias Moura Prazeres et al., 2017). This hints towards the idea that instead of having a common ancestor, pericytes share a mural precursor with the vascular smooth muscle cells (VSMCs) of the tissue in which they reside (Armulik et al., 2011; Majesky et al., 2011). This might explain the relative heterogeneity of pericytes derived from different tissues. Although undetermined in most organs, there is some evidence of this phenomenon in brain pericyte lineage tracing (Etchevers et al., 2001). In vitro studies using pluripotent stem cells (PSCs) have also alluded to a common mural progenitor (Kumar et al., 2017). While the source of pericytes within many organs has been established, the developmental origin of pericytes in skeletal muscle remains elusive.

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2b Pericyte plasticity

Pericytes have several common functions regardless their tissue of origin, namely blood vessel stabilisation and permeability, vascular development/maturation and regulation of blood flow (Armulik et al., 2011; Enge et al., 2002; Hall et al., 2014; Hellstrom et al., 2001; Leveen et al., 1994; Lindahl et al., 1997; Pallone and Silldorff, 2001; Pallone et al., 1998; Peppiatt et al., 2006; Soriano, 1994). In addition, in the last decade many studies have identified pericytes as tissue-resident progenitors able to form multiple human tissues (Dellavalle et al., 2011; Sacchetti et al., 2016). A recent study by Evans and colleagues challenged this view, showing that Tbx18+ mouse pericytes maintain their mural identity and do not generate other cell types in injured and aging tissues, including brain, heart, fat and skeletal muscle (Guimaraes-Camboa et al., 2017). This suggests that plasticity seen in vitro or after transplantation could be an artefact of ex vivo cell culture. The discrepancy between this data and previous studies suggests that mural cells can behave as progenitors but that this behaviour is dependent on the organ and on the developmental stage. Alternatively, it may be that a small population of pericytes with progenitor capabilities do not express Tbx18, and hence were not labelled in the Tbx18-cre strain. This could be possibly due to the heterogeneous nature of pericytes. The model of endogenous pericytes as tissueresident progenitors might therefore need further investigation, perhaps using additional or alternative pericyte lineage-tracing tools (Cano et al., 2017).

Beside their role in supporting the microvasculature and their putative role as tissue progenitors, pericytes can also display tissue-dependent functions [reviewed in (Holm et al., 2018)]. For example, brain pericytes support the blood-brain barrier integrity (Al Ahmad et al., 2011; Armulik et al., 2010; Daneman et al., 2010; Dohgu et al., 2005; Nakagawa et al., 2007) while in the immune system they contribute to the regulation of lymphocyte activation (Balabanov et al., 1999; Fabry et al., 1993; Tu et al., 2011; Verbeek et al., 1995). In skeletal muscle, pericytes contribute to muscle regeneration, fibrosis, fat deposition and ossification [reviewed in (Birbrair et al., 2015; Murray et al., 2017)]. We shall detail later in this chapter the role of pericytes in these processes in the specific context of muscular dystrophies. Generally, pericytes and their associated blood vessels run parallel to muscle fibres, where cross talk is thought to regulate nutrient uptake and postnatal myogenesis. Early studies suggest that pericyte location in capillary vessels of skeletal muscle is fibre type-specific (Gaudio et al., 1985; Levy et al., 2001) and that specific subset of pericytes within skeletal muscle do have distinct roles (Birbrair et al., 2013b). Interestingly, in contrast to the widely excepted view, there is no clear evidence that pericytes can actively alter blood flow in skeletal muscles [reviewed in (Murray et al., 2017; Sims, 1986)].

2c Molecular signature and skeletal muscle-specific pericyte subpopulations

As mentioned above, despite their fundamental roles in health and disease and their ubiquitous presence in all body's tissues and organs, pericytes' identification is made difficult by their heterogeneity, which not only concerns origin and distribution but also the pattern and dynamic of molecular markers they do express (Armulik et al., 2011). In general it can be said that i) none of the pericyte markers are specific; ii) not all pericytes do express all the markers at once; iii) pericytes from different tissues express different markers; iv) marker expression is determined by the developmental and activation stage (Armulik et al., 2011).

Although efforts are being made to characterise skeletal muscle pericytes, many putative markers overlap with other muscle cells and there is no single all-encompassing pericyte-specific marker in skeletal muscle. For this reason and as for other tissues, skeletal muscle pericytes are often identified as much by their anatomical location as by the expression of a pool of molecular markers/proteins [reviewed in (Tedesco et al., 2017)]. However, it is worth mentioning that in sites of active angiogenesis or disorganised tissue, such as dystrophic muscle, it can be difficult to determine which cells are located within the vascular basement membrane and therefore to define the exact location of cells expressing pericyte markers. In addition, the mechanisms regulating pericyte quiescence, activation and their transition between these two states are still unknown, as most studies have focussed on homing factors or determining final fate.

Some of the most common markers used for pericytes are neural-glia antigen 2 (NG2), platelet derived growth factor receptor β (PDGFRβ), smooth muscle α-actin (α-SMA), desmin, CD13, regulator of G protein signalling 5 (RGS5), CD146 and Nestin (Armulik et al., 2011; Birbrair et al., 2011; Tedesco et al., 2017). None of these markers are unique for pericytes. In the skeletal muscle for example, most proteins are expressed in both satellite cells and a subset of muscle pericytes, including Pax3 (Dellavalle et al., 2007; Sacchetti et al., 2016), which may be due to a shared developmental origin (Esner et al., 2006), and Nestin (Birbrair et al., 2011; Day et al., 2007). A subpopulation of non-myogenic muscle pericytes also share the expression of PDGFRα with fibro/adipogenic progenitors (FAPs), a PDGFRα^{+}/CD34^{+}and stem cell antigen-1 (Sca1)$^{+}$ muscle interstitial cell population able to differentiate into myofibroblasts and/or adipose cells (Joe et al., 2010; Uezumi et al., 2010).

Fate-tracing experiments in mice have revealed that a subpopulation of muscle pericytes can have myogenic fate. This includes a subpopulation expressing the alkaline phosphatase (AP), which is able to fuse with developing muscle fibres and enter the satellite cell compartment, both during postnatal development and following acute/chronic muscle injury (Dellavalle et al., 2011). Whether they become *bona fide*, functional satellite cells, however, still needs to be elucidated. In addition, Birbrair et al. used Nestin-GFP/NG2-DsRed double transgenic mice to demonstrate the existence of type-2 (Nestin^{+}/NG2^{+}) and type-1 (Nestin^{-}/NG2^{+}) pericytes. Both populations express the typical pericyte markers PDGFRβ and CD146 and are associated to capillaries. However, type 2 pericytes are able to form myotubes in vitro and in vivo and enter the satellite cell compartment (Birbrair et al., 2013c) while type 1 are PDGFRα^{+} and contribute to fat accumulation and fibrosis (Birbrair et al., 2013b; Birbrair et al., 2013c). A comparison of the AP+ and Nestin+ populations has not been made.

In humans, a subpopulation of AP^{+} interstitial muscle cells associated to small vessels has also been observed (Dellavalle et al., 2007). These human interstitial cells (presumed to be of pericyte origin but obtained from un-purified biopsies) were initially characterised as expressing the pericyte markers AP, desmin, PDGFRβ, vimentin, Annexin V and Integrin b1/CD29, whilst being negative for myogenic genes Pax7 and MyoD, CD31, CD34, NCAM/CD56 and CD45. However, these interstitial cells did not express all pericyte markers; expression of M-cadherin/CD146, NG2 and α-SMA was variable among different preparations (Dellavalle et al., 2007). Moreover, variable expression of NCAM/CD56 and

myogenic regulatory factors in this population has been observed in a subsequent publication (Meng et al., 2011), further contributing to the evidence that this is a variable population in human muscles. In addition, other studies showed that $CD146^+$ subendothelial cells isolated from the postnatal human skeletal muscle microvasculature have high spontaneous myogenic potential in vitro and they generate myotubes and myofibre in vivo (Sacchetti et al., 2016).

Further studies will be needed to address the relationships existing between these different subpopulations of skeletal muscle pericytes from both murine and human origin.

2d Pericytes and satellite cells

Within skeletal muscles, satellite cells are located beneath the basement membranes of muscle fibres and are closely connected with capillary endothelial cells. As a result, a close interaction also occurs between pericytes and satellite cells.

This has led to speculation that there is cross talk between these two cell types (Christov et al., 2007; Dellavalle et al., 2011). This relationship is multi-faceted. For example, the juxta-vascular position of satellite cells is thought to enable co-ordinated angio-myogenesis (Christov et al., 2007), whilst Kostallari et al. found that pericytes directly form a niche for satellite cells, regulating their quiescence and contributing to myogenesis, through Angiopotein 1 and insulin-like growth factor 1 (IGF-1), respectively (Kostallari et al., 2015). Whilst the authors proposed that only $Nestin^+$ type-2 pericytes were involved in these processes, future lineage-tracing experiments and selective ablation of type-1 or type-2 subtypes are required to give us a clear answer on this matter.

The relationship between pericytes and satellite cells/myoblasts might even be more complex that the one just described above. Several years ago, Cossu and Bianco proposed that during development, cells associated to the growing vessels might be recruited to adopt the local fate of the specific tissue they were invading. In the case of the skeletal muscle, cells associated to the blood vessels that enter the muscle anlagen might be recruited to adopt a myogenic fate and contribute to its histogenesis (Bianco and Cossu, 1999). This concept found a first and partial confirmation in the finding that the embryonic dorsal aorta contains skeletal myogenic cells, named mesoangioblasts, that co-express endothelial and myogenic markers and can contribute to muscle regeneration (De Angelis et al., 1999; Minasi et al., 2002). In vitro co-cultures of embryonic dorsal aortas and murine myotubes demonstrated that Noggin secreted from newly formed muscle fibres recruits $NG2^+$ dorsal aorta progenitors and promotes their conversion to a myogenic fate. Conversely, myogenesis is inhibited by bone morphogenetic factor 2 (BMP2) expressed by the aorta (Ugarte et al., 2012). This data indicates that skeletal muscle and blood vessels compete to recruit mesodermal progenitor cells to a myogenic or to a perivascular fate during foetal muscle development and that the final decision of which cell fate to adopt might be due to the balance existing between Noggin and BMP2 expression. These data also suggest that a fate switch might happen also in the other direction, with skeletal myoblasts being recruited to a pericyte fate. In this direction, Cappellari et al. showed that exposure of both embryonic and foetal skeletal myoblasts to Notch Delta ligand 4 (Dll4), expressed by the developing endothelium (Kume, 2012), and PDGF-BB, which recruits pericytes from the surrounding

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mesenchyme (Hellstrom et al., 1999), downregulate myogenic genes, upregulate pericyte markers and bring myoblasts to assume a perivascular position when co-cultured with endothelial cells. Moreover, they showed that myoblasts occasionally adopt a perivascular position also in vivo, ruling out that the direct conversion of skeletal myoblasts into pericytes is simply an artefact of ex vivo cell manipulations (Cappellari et al., 2013). Altogether, this data suggests that the endothelium, via Dll4 and PDGF-BB expression, might induce a fate switch in adjacent skeletal myoblasts. Cossu and Cappellari postulated that the reason for this lineage promiscuity between muscle cells and perivascular cells might be explained by developmental timing and the specific need of the skeletal muscle tissue during histogenesis: for the muscle to grow, it recruits not only myoblasts but also unorthodox mesodermal cells that once exposed to muscle-specification molecules undergo myogenesis; once the muscle is grown, hypoxia is triggered with consequent vascular endothelial growth factor release and activation of angiogenesis, with developing blood vessels in the muscles recruiting supporting perivascular cells from the surrounding mesoderm (Figure 1) (Cappellari et al., 2013; Cappellari and Cossu, 2013). Recent work in our laboratory has demonstrated that this mechanism is also conserved in adult murine and human satellite cell-derived myoblasts, and that it can be exploited to enhance migration of myoblasts when transplanted (Gerli et al., 2019).

3 Pericytes contribution to muscle regeneration

3a Pericytes as stem/progenitor cells for muscular dystrophies

Stem cell transplantation therapies for muscular dystrophies have long been touted as a method to improve clinical features. Satellite cell-derived myoblasts were initially considered the ideal candidate cell population for the cell therapy of muscular dystrophies (Partridge et al., 1989). However, successive clinical studies have revealed that although some level of dystrophin was produced, no efficacy was achieved in patients with Duchenne Muscular dystrophy (DMD), one of the most severe and common form of muscular dystrophy [reviewed in (Negroni et al., 2016; Partridge, 2000; Tedesco et al., 2010)]. While researchers tried to identify the possible culprit(s) for this result (Fan et al., 1996; Guerette et al., 1997; Huard et al., 1992; Skuk and Tremblay, 2011) and find possible therapeutic solutions (Arpke et al., 2013; Boldrin et al., 2012; Cerletti et al., 2008; Collins et al., 2005; Gilbert et al., 2010; Montarras et al., 2005; Morales et al., 2013; Palmieri et al., 2010; Rocheteau et al., 2012; Sacco et al., 2008; Skuk et al., 2006; Skuk et al., 2007; Skuk et al., 2004; Smythe et al., 2000; Tanaka et al., 2009), the search was started for alternative cell types that could be effective in cell therapy protocols for muscle. Whilst several candidate stem/progenitor populations have been identified as contributing to skeletal muscle regeneration [reviewed in (Loperfido et al., 2015; Negroni et al., 2016; Tedesco et al., 2010; Tedesco et al., 2017)], pericyte-derived cells seem to hold a preferential place.

Data obtained from different laboratories in the past years now support an important role for myogenic pericytes in skeletal muscle regeneration. As mentioned earlier in this chapter, fate-tracing of AP^+ murine skeletal muscle pericytes reveals how this subset of pericytes contribute to the formation of new muscle fibres in a limb girdle muscular dystrophy (LGMD) 2D mouse model (Dellavalle et al., 2011). In human skeletal muscle, AP^+ pericytes

are increased in muscle biopsies of some dystrophic patients compared to healthy controls and neuropathic patients (myopathic 9.4% vs and controls 4.7% vs neuropathic 5.7%) (Diaz-Manera et al., 2012). These results are supported by another study showing an increase in the population of $NG2^+$ pericytes in acute muscular injury (Valero et al., 2012). Conversely, we have reported a significant decrease (of approximately 55%) in the numbers and myogenic capacity of AP^+ muscle pericytes both in mice and patients with LGMD2D (Tedesco et al., 2012). This apparently contrasting data could be explained by the different stage of disease progression of the biopsies/samples used in these two studies. We propose that in dystrophic muscles, during the first phase of muscle degeneration/regeneration AP^+ skeletal muscle pericytes are transiently amplified to sustain the continuous need for new muscle fibres in cooperation with satellite cells and other muscle stem cells. Over time cycles of muscle degeneration/regeneration lead to an exhaustion of the pool of AP^+ pericytes.

Myogenic pericyte transplantation has also been tested in pre-clinical models of muscular dystrophies, where they have the advantageous characteristic of being deliverable through the arterial circulation. These reports show active contribution of pericytes to muscle regeneration in dystrophic animal models, (Berry et al., 2007; Bonfanti et al., 2015; Dellavalle et al., 2007; Diaz-Manera et al., 2010; Domi et al., 2015; Galvez et al., 2006; Iyer et al., 2018; Minasi et al., 2002; Morosetti et al., 2011; Pessina et al., 2012; Quattrocelli et al., 2014; Sampaolesi et al., 2006; Sampaolesi et al., 2003; Sciorati et al., 2006; Tedesco et al., 2011).

As with other myogenic progenitor populations, one of the major hurdles to improve the feasibility of pericytes as a transplantation therapy for muscular dystrophy is the low level of engraftment. Recently, a first-in-human phase I/II clinical trial based upon intra-arterial transplantation of HLA-matched allogeneic pericyte-derived mesoangioblast in 5 DMD boys showed that whilst relatively safe, there was limited dystrophin production (1 of 5 biopsies), probably due to low level of cell engraftment (Cossu et al., 2015). Optimisation of this methodology is therefore required for future therapeutic use.

Lastly, Zazt and colleagues investigated the effect of repeated intra-peritoneal injections of adipose human pericytes on lifespan and motor function of a severe DMD mouse model. They reported that adipose tissue-derived pericytes led to an increased life-span of one month, possibly mediated by immune modulation rather than a regenerative ability (Valadares et al., 2014). In view of the unusual delivery route (intraperitoneal), the lack of histological evidence of engraftment or amelioration of tissue morphology and that none of the functional tests revealed differences between the groups, additional evidence would be required to assess the feasibility and clinical relevance of this strategy.

3b Limitations to cell therapy and possible solutions

Despite numerous pre-clinical and clinical cell therapy studies on cell transplantation, muscular dystrophies still remain incurable, and there are still several challenges to be addressed before becoming routinely used in a clinical setting, including engraftment efficacy, transplantation route and modulation of the immune response [reviewed in (Maffioletti et al., 2014; Negroni et al., 2016)]. The main challenge is due to the fact that

skeletal muscle is the most abundant human tissue, covering 30-38% of total body weight (Janssen et al., 2000). Transplanting stem cells has been shown to result in clinical improvement when specific muscles are affected, such as the recent trial for oculopharyngeal muscular dystrophy using intramuscular injections of autologous myoblasts (Perie *et al.*, 2014). However, replacing large volumes of dystrophic muscle affected in widespread muscular dystrophies (such as DMD) would require the successful engraftment of billions of myogenic progenitors. Indeed, as with other myogenic progenitor populations, there are two major hurdles need to be overcome in order to improve the feasibility of pericytes and pericyte-derived cells as a transplantation therapy for muscular dystrophies: i) the low levels of cell engraftment to the dystrophic muscle and ii) the limited cell expansion potential in vitro.

In this direction, several strategies have been developed with the aim to improve homing and engraftment of pericyte-derived cells. These include making blood vessels more accessible for cell extravasation (Giannotta et al., 2014), treating them with homing factors (Quattrocelli et al., 2014) and modulating the immune response (Maffioletti et al., 2014; Noviello et al., 2014)., Exposure to cytokines and integrins can also improve pericyte-derived mesoangioblast engraftment (Galvez et al., 2006; Palumbo et al., 2004; Tagliafico et al., 2004). However, it is important to assess possible side effects of transplanting engineered cells, as whilst they can promote extravasation and homing, the expression of different surface molecules could modulate the immune response following transplantation, including deleteriously increasing donor cell clearance. The interaction between muscle or pericytes and immune cells via adhesion molecules is well-documented [reviewed in (Maffioletti *et al.*, 2014)(Noviello et al., 2014)]. Of interest, intracellular adhesion molecule 1 (ICAM-1/CD54) expression is increased in inflamed endothelial cells and muscle fibres (Bartoccioni et al., 1994; Tews and Goebel, 1995). However, leukocyte function-associated antigen 1 (LFA-1) expressed on T cells binds to ICAM-1, resulting in cytotoxic T cell infiltration (Bartoccioni *et al.*, 1994). Also, expression of VCAM-1 and its ligand VLA-4 have been observed in muscle capillaries and infiltrating cells of patients with inflammatory myopathies (Tews and Goebel, 1995). Interestingly, VCAM-1 expression is associated with increased engraftment of CD133+ cells, another class of myogenic vessel-associated cells, which have been transplanted intra-arterially into dystrophic mice (Gavina et al., 2006). In this paper, Gavina and colleagues found that VCAM-1 expression in muscle capillaries increased after exercise and increased engraftment, whilst conversely, blocking VCAM-1 expression significantly reduced engraftment (Gavina et al., 2006). In summary, careful assessment of the transplant population and donor muscle tissue should be performed to maximise engraftment.

Another important factor for optimal muscle cell therapy is the ability of myogenic cells to proliferate in vitro and produce large numbers of transplantable progenitors. This point is of particular importance as in muscular dystrophies the myogenic cells (including pericytes) are exhausted or defective (Blau et al., 1983; Cassano et al., 2011; Kudryashova et al., 2012; Sacco et al., 2010; Tedesco et al., 2012). To overcome the limitation of expansion potential from biopsy-derived cells, induced pluripotent stem cells (iPSCs) can be differentiated towards the myogenic lineage. One such protocol developed by our group is to produce iPS-derived mesoangioblast-like cells, which have an unlimited proliferative potential, which

could then efficiently be induced to skeletal myogenesis with a short expression of the myogenesis regulator MyoD (Gerli et al., 2014; Maffioletti et al., 2015; Tedesco et al., 2012).

Another strategy to extend the proliferative potential of pericyte-derived mesoangioblasts is to provide them with an indefinite lifespan via expression of immortalising genes. Our group has recently shown that reversibly immortalising lentiviral vectors expressing the catalytic subunit of human telomerase hTERT and the polycomb gene Bmi-1 is safe and efficacious at extending the proliferative capacity of human DMD pericyte-derived mesoangioblasts, enabling them to have a human artificial chromosome containing the whole dystrophin locus (DYS-HAC) transferred (Benedetti et al., 2018). After DYS-HAC transfer, genetically-corrected DMD pericyte-derived clones were expanded to reach a number of cells potentially sufficient to treat a DMD paediatric patient [in the range of 10^9cells; (Benedetti et al., 2018; Cossu et al., 2015)].

In the quest for an ideal cell type for muscle cell therapy, our group also explored a different approach by taking advantage of the findings that embryonic and foetal myoblasts could be converted to the pericyte fate following activation of Notch and PDGF pathways via Dll4 and PDGF-BB (Cappellari et al., 2013; Cappellari and Cossu, 2013). As mentioned earlier in this chapter, adult murine and human satellite cell-derived myoblasts exposed to Dll4 and PDGF-BB also acquired perivascular cell features, including transendothelial migration ability, whilst maintain myogenic capacity (Gerli et al., 2019). We propose that this strategy could generate a hybrid pericyte-myoblast cell retaining the two peculiar characteristics of both cell types: the ability to generate muscle with high efficacy (myoblast) alongside transendothelial migration capacity (pericyte-derived cells).

In conclusion, there are several promising strategies in development using pericyte-like cells for cell therapy of muscular dystrophies. Nevertheless, it is crucial that both the transplanted cell and the host environment are considered in order to improve engraftment efficacy. Therefore, it is likely that future clinical experimentation will focus on combined therapies, where stem cell transplantation is merged with another therapeutic intervention, such as administration of anti-fibrotic and pro-angiogenic drugs, which have been shown to improve pathology in mouse models of muscular dystrophy (Cordova et al., 2018; Gargioli et al., 2008).

4 Non-myogenic role of skeletal muscle pericytes

4a Pericyte contribution to fat accumulation

Intramuscular deposition and accumulation of adipose tissue deposition is a typical hallmark of disease progression and severity in muscular dystrophies, especially in DMD (Lukjanenko et al., 2013; Mankodi et al., 2016; Wren et al., 2008). Pericytes from different tissues, including skeletal muscle, have shown adipogenic potential when cultured in vitro (Crisan et al., 2008a; Farrington-Rock et al., 2004; Minasi et al., 2002). In the skeletal muscle, a subset of quiescent cells expressing the adipogenic progenitor marker PDGFRα are closely associated to the vasculature and located in the interstitial space between muscle fibres. Following muscle injury, these cells, later called fibro/adipogenic progenitors (FAPs),

exit quiescence, start proliferating and contribute to ectopic fat accumulation in skeletal muscle (Joe et al., 2010; Rodeheffer, 2010; Uezumi et al., 2010). Other groups have demonstrated that PDGFRα$^+$ type-1 but not PDGFRα$^-$ type-2 pericytes have adipogenic potential in vitro (Birbrair et al., 2013a; Gautam et al., 2017). Moreover, cultured type-1 pericytes generated ectopic white fat when delivered intramuscularly in a mouse model of fatty degeneration (Birbrair et al., 2013a). Future lineage-tracing studies might clarify whether type-1 pericytes do indeed contribute to fat accumulation in skeletal muscle in situ. In addition, a recent lineage-tracing study by Strickland and colleagues demonstrated that PDGFRβ$^+$ skeletal muscle pericytes were able to differentiate into perilipin$^+$ adipocytes in a congenital muscular dystrophy model (Yao et al., 2016).

4b Pericyte contribution to chondrogenesis

In addition to committing to a myogenic fate, pericytes have been shown to undergo chondrogenic and osteogenic differentiation in vitro (Crisan et al., 2008b; Farrington-Rock et al., 2004; James et al., 2012; Levy et al., 2001; Zhang et al., 2011). Whether pericytes contribute to skeletal muscle ossification in vivo, however, remains undetermined. Interestingly, ectopic calcification has been reported in animal models of DMD including the mdx mouse (Geissinger et al., 1990) and dog (Nguyen et al., 2002). Additionally, it has recently been shown that AP$^+$ pericytes are reduced in immune-deficient scgb/Rag2/gc-null mice (a model of LGMD2E), whilst calcification of skeletal muscles is increased (Giovannelli et al., 2018). Unsurprisingly, this has led to the implication that pericytes are involved in the ectopic calcification of blood vessels in skeletal muscle, especially in the context of ongoing angiogenesis [reviewed in (Collett and Canfield, 2005)]. Of note, AP$^+$ mononuclear interstitial cells from adult human skeletal muscle have been shown to express the osteogenic marker osteocalcin when cultured in vitro (Levy et al., 2001), and in fibrodysplasia ossificans progressiva (FOP), progressive ossification of skeletal muscle has been shown to be caused by mesenchymal-like stromal cells expressing smooth muscle markers (Hegyi et al., 2003). Whilst the authors postulate that these cells are pericytes, more recent data suggests it may be due to the Tie2$^+$ FAP population (Lees-Shepard et al., 2018). Again, this points to the requirement for the differentiation between subpopulations of FAPs and pericytes to be properly determined.

4c Pericytes and fibrosis

Increased fibrosis is a typical feature of aged and dystrophic muscles, which ultimately results in muscle weakness, atrophy and reduction of its regenerative potential (Kragstrup et al., 2011; Mann et al., 2011; Ryall et al., 2008; Thompson, 2009; Walston, 2012). A major contributor to fibrosis is the myofibroblast (Duffield et al., 2013; Humphreys et al., 2010; Lin et al., 2008; Quan et al., 2006; Willis et al., 2006; Wynn, 2008; Zeisberg et al., 2007). Myofibroblasts are responsible for the production and deposition of collagenous extracellular matrix, with consequent reduction of muscle fibre contractility, disruption of the muscle structure and eventually skeletal muscle dysfunction. Several putative myofibroblast progenitor populations have been associated to muscle fibrosis, including FAPs and cells expressing PDGFRα (Uezumi et al., 2010) and ADAM12 (Dulauroy et al., 2012). As some of these markers are also expressed by pericytes, it has been hypothesized that pericytes may be a source of myofibroblasts during skeletal muscle fibrosis. Indeed,

Birbrair et al. showed that skeletal muscle PDGFRα$^+$ pericytes are fibrogenic in vitro when cultured in presence of transforming growth factor β (TGFβ), while in vivo they produce collagen, responsible for increasing skeletal muscle fibrosis in old mice (Birbrair et al., 2014; Birbrair et al., 2013c).

In parallel, using a complex triple transgenic mouse that expressed tetracycline under ADAM12 locus, Cre recombinase under control of the tetracycline transactivator and the conditional reporter Rosa26floxSTOP-YFP, Dulauroy et al. showed the existence of a transient subpopulation of ADAM12$^+$ interstitial cells that become active after muscle injury. With this approach they revealed that the large majority of collagen-producing myofibroblasts were generated starting from ADAM12$^+$ cells, which are located in a perivascular position and are positive for PDGFRβ. Moreover, ablation of ADAM12$^+$ cells reduced the number of pro-fibrotic cells and collagen accumulation (Dulauroy et al., 2012). This data corroborates the hypothesis that in skeletal muscle ADAM12 identifies a myofibroblast progenitor with pericyte characteristics.

4d Pericyte role in the vascular compartment

Muscle ischemia has been observed in biopsies from patients with DMD for many decades (Engel, 1967) and clinical symptoms were once hypothesised to be caused by local infarctions. Whilst there have not been consistent reports in changes to blood flow or microvascular architecture observed in DMD patients [reviewed in (Thomas, 2013)], it has been shown that dystrophin-deficient muscle fibres are more susceptible to muscle ischemia though a neuronal nitric oxide synthase μ (nNOSμ)-specific mechanism. Localised muscle ischemia results in increased exercise-induced fatigue and micro-vessel constriction, elevating clinical symptoms (Kobayashi et al., 2008). This mechanism is not specific to DMD; changes to sarcolemmal nNOS expression have been observed in biopsies from other several muscular dystrophies including limb-girdle and congenital muscular dystrophy (Kobayashi et al., 2008). Whether or not pericytes actively contribute to the vascular pathology observed in muscular dystrophies, it has been shown that improving reduced blood flow improves clinical symptoms and cell therapy in pre-clinical models (Brunelli et al., 2007; Gargioli et al., 2008). Of note, treatment of dystrophic mice with nitric oxide releasing drugs improves the efficacy of mesoangioblast transplantation (Brunelli et al., 2007).

5 Derivation of pericytes from pluripotent stem cells

Pluripotent Stem Cell (PSC)-derived cells are of great importance for studying development and organogenesis, whilst also being promising candidates for cell transplantation studies, due to their unlimited expansion potential. Differentiating PSCs into pericyte-like cells enables the possibility to study developmental relationships between mural cells of different developmental origins. For example, Kumar et al. found using clonal analyses that mesodermal-derived progenitors could make mesenchymal stromal cells, VSMCs and pericytes (Kumar et al., 2017). Additionally, this protocol was used to derive arteriolar and capillary subtypes of pericytes through the modulation of growth factors. Protocols to differentiate vascular cells from different embryonic lineages (neural crest, lateral plate

mesoderm and paraxial mesoderm) have also been developed in order to study different forms of vascular development (Cheung et al., 2012; Chin et al., 2018; Cochrane et al., 2018; Orlova et al., 2014). In muscle pathology, PSC-derived pericyte-like cells have shown pathological improvement in pre-clinical models of muscular dystrophy (Tedesco et al., 2012) and ischemia (Dar et al., 2012). Determining whether PSC-derived cells are truly functional pericytes when transplanted in vivo is difficult. However, using lineage determinants to produce a pericyte-like mesenchymal (or neural ectodermal) progenitor, which when transplanted differentiates into a regeneration-supporting cell, could be a more feasible option.

Concluding Remarks

Since their initial description there has been important progress in understanding pericyte biology and function; however, their exact role and involvement in the pathogenic process of muscle degeneration and regeneration is still in need of a definitive model. Nonetheless, the clinical relevance of pericyte is now more important than ever before, both as a target for possible therapeutic intervention (e.g. reduction of fibrosis) or as advanced therapy medicinal products. We foresee that in the upcoming decade the ontogeny and characteristics of this elusive cell type will become clearer, setting the foundation for their organotypic derivation from human pluripotent cells and use in next-generation experimental therapies for muscle diseases.

Acknowledgments

We thank Giulio Cossu for the critical reading of this manuscript. This research was supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the National Institute for Health Research (NIHR) or the Department of Health. Work in the Tedesco laboratory is funded by the European Research Council (7591108 – HISTOID), Muscular Dystrophy UK, the UK MRC and BBSRC and the AFM-Telethon. F.S.T. is also grateful to previous funding from the European Union's 7th Framework Programme for research, technological development and demonstration under grant agreement no. 602423 (PluriMes), Fundació La Marató de TV3, IMI joint undertaking n° 115582 EBiSC (EU FP7 and EFPIA companies), Duchenne Parent Project Onlus, Takeda New Frontier Science and the NIHR (Academic Clinical Fellowship in Paediatrics ACF-2015-18-001). L.A.M. is supported by the Human Frontiers Science Program.

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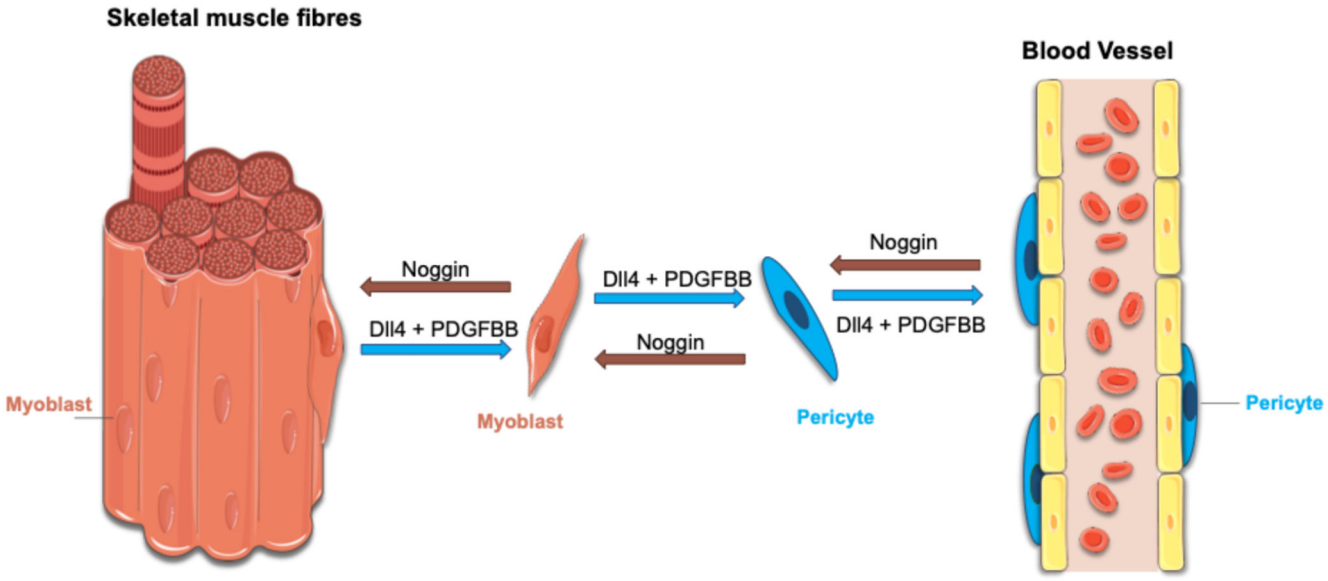

Figure. 1.

A schematic representation of the hypothetical model explaining lineage promiscuity between muscle pericytes and satellite-cell derived myoblasts during development. The figure has been generated using Servier Medical Art.