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**Regulation and phylogeny of skeletal muscle regeneration**

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**Abstract**

One of the most fascinating questions in regenerative biology is why some animals can regenerate injured structures while others cannot. Skeletal muscle has a remarkable capacity to regenerate even after repeated traumas, yet limited information is available on muscle repair mechanisms and how they have evolved. For decades, the main focus in the study of muscle regeneration was on muscle stem cells, however, their interaction with their progeny and stromal cells is only starting to emerge, and this is crucial for successful repair and re-establishment of homeostasis after injury. In addition, numerous murine injury models are used to investigate the regeneration process, and some can lead to discrepancies in observed phenotypes. This review addresses these issues and provides an overview of some of the main regulatory cellular and molecular players involved in skeletal muscle repair.

Key words: skeletal muscle, regeneration, stem cells, evolution, quiescence, injury

**Introduction**

The ability to regenerate tissues and structures is a prevalent feature of metazoans although there is significant variability among species ranging from limited regeneration of a tissue (birds and mammals) to regeneration involving the entire organism (cnidarians, planarians, hydra). The intriguing evolutionary loss of regenerative capacity in more complex organisms highlights the importance of identifying the underlying mechanisms responsible for these diverse regenerative strategies. One of the most studied tissues that contributes to new appendage formation is skeletal muscle, thereby making it a major focus of regeneration studies during evolution. The emergence of new lineage-tracing tools in different animal models has permitted the identification of specific progenitor cell populations and their contribution to tissue repair.

Skeletal muscles allow voluntary movement and they play a key role in regulating metabolism and homeostasis in the organism. In mice and humans this tissue represents about 30-40% of the total body mass. This tissue provides an excellent tractable model to study regenerative myogenesis and the relative roles of stem and stromal cells following a single, or repeated rounds of injury. Although muscle regeneration relies mainly on its resident muscle stem (satellite) cells (MuSCs) to effect muscle repair, interactions with neighbouring stromal cells, by direct contact or via the release of soluble factors, is essential to restore proper

function. Each step of the myogenic process is regulated by specific regulatory factors including extrinsic cues, yet the nature and source of these signals remain unclear. This review will address these issues and discuss the different experimental models used to investigate the regenerative process.

### **Prenatal and postnatal skeletal muscle development**

In amniotes, skeletal muscles in the limbs and trunk arise from somites through a series of successive waves that include embryonic and foetal phases of myoblast production (Biressi et al., 2007; Comai and Tajbakhsh, 2014). In response to key transcription factors, committed embryonic and foetal myoblasts align and fuse to generate small multinucleated myofibres during primary myogenesis in the embryo (from E11-E14.5), then myofibres containing hundreds of myonuclei during secondary myogenesis (from E14.5-to birth). During the early and late perinatal period that lasts about 4 weeks, continued myoblast fusion, or hyperplasia, is followed by muscle hypertrophy (Sambasivan and Tajbakhsh, 2007; Tajbakhsh, 2009; White et al., 2010). During adulthood, skeletal muscle is associated with little proliferative activity and generally returns to homeostasis about 1 month following injury.

Emerging MuSCs are found underneath a basement membrane from about 2 days before birth in mice and they continue to proliferate until mid-perinatal stages. The majority of quiescent MuSCs are established from about 2-4 weeks after birth (Tajbakhsh, 2009; White et al., 2010). During prenatal and postnatal myogenesis, stem cell self-renewal and commitment are governed by a gene regulatory network that includes the paired/homeodomain transcription factors Pax3 and Pax7, and basic helix-loop-helix (bHLH) myogenic regulatory factors (MRFs), Myf5, Mrf4, Myod and Myogenin. Pax3 plays a critical role in establishing MuSCs during embryonic development (except in cranial-derived muscles) and Pax7 during late foetal and perinatal growth. Indeed, *Pax3:Pax7* double mutant mice exhibit severe hypoplasia due to a loss of stem and progenitor cells from mid embryonic stages, and these *Pax* genes appear to regulate apoptosis (Relaix et al., 2006; Relaix et al., 2005; Sambasivan et al., 2009). During perinatal growth, *Pax7* null mice are deficient in the number of MuSCs and fail to regenerate muscle after injury in adult mice (Lepper et al., 2009; Oustanina et al., 2004; Seale et al., 2000; von Maltzahn et al., 2013). The absolute requirement for MuSCs was shown by genetic elimination of satellite cells postnatally, which resulted in failed regeneration (Lepper et al., 2011; Murphy et al., 2011; Sambasivan et al., 2011).

The MRFs bind to consensus sites located in regulatory sequences of target genes to activate muscle-specific gene expression. Experiments using simple or double knockout mice have shown the temporal and functional roles of these different factors during myogenesis. *Myf5*, *Mrf4* and *Myod* assign myogenic cell fate of muscle progenitor cells to give rise to myoblasts (Kassar-Duchossoy et al., 2004; Rudnicki et al., 1993; Tajbakhsh et al., 1996) whereas *Myogenin* plays a crucial role in myoblast differentiation prenatally (Hasty et al., 1993) but not postnatally as the conditional mutation of *Myogenin* in the adult has a relatively mild phenotype (Knapp et al., 2006; Meadows et al., 2008; Venuti et al., 1995). In the adult, *Myod* deficient mice that survive have increased precursor cell numbers accompanied by a delay in regeneration (Megeney et al., 1996; White et al., 2000); whereas *Myf5* null mice showed a slight delay in repair (Gayraud-Morel et al., 2007). These studies suggested that *Myf5*, *Mrf4* and *Myod* could in some cases have compensatory roles, but that robust regeneration requires all three MRFs. Interestingly, additional transcription factors have been shown to interact with MYOD to regulate myogenesis. For instance, ChiP-seq data demonstrated that KLF5 (Kruppel-like factor, member of a subfamily of zinc-finger transcription factors) (Hayashi et al., 2016) as well as RUNX1 (Umansky et al., 2015) binding to *Myod*-regulated enhancers is necessary to activate a set of myogenic differentiation genes. It is likely MRFs combined with other transcription factors fine-tune the myogenesis process and it would be important to explore further the set of co-activators/repressors required for each step of muscle repair.

### **Crucial regulators of muscle regeneration**

Genetic compensatory mechanisms and MuSC heterogeneity highlight the complexity of the regulatory network governing each phase of prenatal and postnatal myogenesis. Notably, some regulators have been identified as essential for MuSCs behaviour and by consequence also for muscle regeneration. *Pax7* is one critical postnatal regulator as its depletion (*Pax7*<sup>-/-</sup>) results in a progressive loss of satellite cells during homeostasis and following injury (Gunther et al., 2013; Seale et al., 2000; von Maltzahn et al., 2013). This finding also typifies the relatively long lag in observed phenotypes during homeostasis following removal of a critical regulator, compared to proliferating myogenic cells.

The Notch signalling pathway is another crucial regulator of satellite cells as the specific depletion of RBPJ, the DNA binding factor essential for mediating canonical Notch signalling, induces a spontaneous differentiation and a loss of MuSCs during quiescence, and

following injury (Bjornson et al., 2012; Mourikis et al., 2012). Notch receptors are expressed at the cell surface and its ligands, Delta-like ligand (Dll1, 4) and Jagged (JAG1, 2) are presumably provided by the myofibre. Binding of ligand to the receptor results in cleavage of Notch (ADAM and  $\gamma$ -Secretase proteases), and release of Notch IntraCellular Domain (NICD) to the nucleus where it binds RBPJ to activate immediate target genes, notably the transcription factors *HeyL*, *Hes1* and *Hesr1/3* (Castel et al., 2013; Jarriault et al., 1995; Kopan and Ilagan, 2009). Intriguingly, the double *Hesr1* and *Hesr3* knock-out triggers a progressive loss of MuSCs (<20% in 20weeks) similar to RBPJ depletion (Fukada et al., 2011) whereas the absence of Notch3 receptor (*Notch3*<sup>-/-</sup>) results in an increase in satellite cell number (+140% in 4months) (Kitamoto and Hanaoka, 2010). Surprisingly, overexpression of NICD in MuSCs induces a fate switch from myogenic to brown adipogenic lineage (*Pax7*<sup>CT2/+</sup>; *R26*<sup>stop-NICD</sup>), while it rescues the loss of satellite cells in adult *Pax7*-deficient mice (*Pax7*<sup>CT2/flox</sup>; *R26*<sup>stop-NICD</sup>) (Pasut et al., 2016). In addition, aged (*Tg:MCK-Cre*; *R26*<sup>stop-NICD</sup>) and dystrophic mice (*Tg:MCK-Cre*; *R26*<sup>stop-NICD</sup>; *mdx*) that experienced NICD specifically in myofibres improve muscle function and repair (Bi et al., 2016).

Several studies have shown that activation of the expression of a set of evolutionary conserved microRNAs (miRNAs) that function as post-transcriptional regulators, results in precise cellular responses in developmental, physiological, and pathological conditions (Williams et al., 2009). miRNAs are a class of endogenous, single-stranded, non-coding RNAs of about 20-23 nucleotides in length that bind to the 3' untranslated region (3'UTR) of their target mRNAs, resulting in either inhibition of protein translation or degradation of the targeted messenger RNA (mRNA) (Bartel, 2004). miRNAs are transcribed as double-stranded primary miRNA that is cleaved by Drosha (endonuclease) into a pre-miRNA. After nuclear export, Dicer (endonuclease) generates the mature miRNA that is incorporated into the RISC complex (Bartel, 2004; Finnegan and Pasquinelli, 2013; Pasquinelli, 2012). Profiling of whole *Tibialis anterior* (TA) muscle and MuSCs by small RNA-seq identified dynamic expression of specific miRNAs characterizing muscle regeneration (Aguilar et al., 2016) (Castel et al. submitted). The essential role of miRNAs in skeletal muscle regeneration has been demonstrated by conditional deletion of *Dicer* in *Pax7*<sup>+</sup> cells resulting in their depletion (<20%) and a quasi-absence of repair following injury (Cheung et al., 2012). Although numerous miRNAs have been reported to regulate myoblast proliferation and differentiation (Kirby et al., 2015), only one miRNA, miR-489 (Cheung et al., 2012)) has been reported to regulate MuSC quiescence and/or self-renewal.

Long non-coding RNAs (lncRNAs) constitute a recently defined class of transcripts in several tissues with major roles in normal physiology as well as development, embryonic stem cell maintenance, and disease (Fatica and Bozzoni, 2014; Neguembor et al., 2014). LncRNAs are transcribed by RNA polymerase II and undergo splicing, capping and polyadenylation (Derrien et al., 2012). Similarly to miRNAs, RNA-seq revealed specific lncRNA signatures that dynamically evolve with muscle repair (Aguilar et al., 2016) and disease (Neguembor et al., 2014). Moreover, lncRNAs have been shown to be critical for myogenic differentiation by regulating *Myod* transcriptional activity (Yu et al., 2017), decay of specific differentiation miRNAs (Cesana et al., 2011) or by inhibition of translation (Gong et al., 2015). However, only a few functionally conserved lncRNAs have been identified, and *in vivo* gain/loss of function studies are largely lacking for this important class of regulators. Interestingly, LINC00961 was recently reported to generate a small polypeptide called SPAR that acts via the lysosome following starvation and amino-acid-mediated stimulation to suppress mTORC1 activity (Matsumoto et al., 2017; Tajbakhsh, 2017). This novel pathway modulates skeletal muscle regeneration following injury thereby linking lncRNA encoded polypeptide function to stress response following tissue damage.

A variety of intrinsic signals has been proposed to modulate muscle repair, but more recently extrinsic and biomechanical cues have emerged as equally crucial for MuSC regulation and regeneration. Skeletal muscle stiffness, defined by the elastic modulus of  $\approx 12$  kPa, is altered during aging, disease or following injury (Cosgrove et al., 2009). Similarly, in *Col6a1*<sup>-/-</sup> mice that model Bethlem myopathy and Ullrich congenital muscular dystrophy, muscle regeneration is severely compromised after (triple) injury, and this is associated with decreased muscle stiffness to  $\approx 7$  kPa (Urciuolo et al., 2013). Interestingly, engraftment of wild-type fibroblasts partially restores COLVI, muscle stiffness, and by consequence muscle repair. These observations were consistent with a previous study showing the increase of regenerative potential of satellite cells following culture on a substrate that recapitulates the rigidity of muscle tissue compared to plastic ( $\approx 10$  kPa) (Gilbert et al., 2010). In addition, extracellular matrix (ECM) proteins are critical components of the MuSC microenvironment and they undergo gradual remodelling from foetal to adult stages, and during ageing (Chakkalakal et al., 2012; Tierney et al., 2016). For example, fibronectin (Fn) is transiently expressed in activated satellite cells (5dpi) (Bentzinger et al., 2013) and it decreases in aged



mice (Lukjanenko et al., 2016). Interestingly, direct injection of Fn in injured aged mice showed improved muscle repair (Lukjanenko et al., 2016). Moreover, how MuSCs sense their microenvironment is also critical for effective function as shown by the restoration of  $\beta$ 1-integrin in old and *mdx* mice leading to satellite cell expansion and muscle repair by enhancing MuSCs connectivity to the ECM (Rozo et al., 2016). Notably, among the intrinsic/extrinsic factors investigated thus far, only a few were reported to dramatically diminish or deplete the satellite cell population thereby highlighting the robustness of muscle regeneration.

### Choosing the appropriate regeneration model

The various phases of muscle repair have been well described (Laumonier and Menetrey, 2016). However, a plethora of acute and chronic injury models are used to investigate the regenerative process without a concerted discrimination among these models. Notably, the regeneration phenotype of the *Myf5* null mice varied in different injury models: both toxin (Cardiotoxin) and freeze injury induce a delay in regeneration, however, fibrosis and adipocyte infiltration was significantly increased only following the physical injury (Gayraud-Morel et al., 2007).

Furthermore, the sampling time after injury is also essential to fully score a regeneration phenotype: the extend of new muscle formation after different types of trauma (such as anaesthetic (Sadeh, 1988), denervation (Shavlakadze et al., 2010) or toxin injury (Collins et al., 2007)) is similar at 4 weeks in young (8weeks) versus geriatric (30months) individuals, whereas the delay in the onset of myogenesis observed at earlier time points (5-14 days post-injury) could be underestimated (Conboy et al., 2005). Furthermore, the endpoint of muscle regeneration, about 4 weeks after trauma, is generally based on histological criteria such as the presence of centrally nucleated fibres and self-renewed quiescent MuSCs. However, remodelling might continue to occur after this period; it is interesting to note that the number of satellite cells increases by 2-3 fold up to 3 months following a single round of injury (Hardy et al., 2016). Similarly, the injury induces an increase in the number of vessels/fibre that persists 6 months after trauma. Therefore quantifications of additional features are necessary to fully monitor the regeneration process. Here too it should be noted that the vast majority of studies on muscle regeneration are performed on the TA muscle. Given the genetic and phenotypic differences between muscles in different anatomical locations (Sambasivan et al., 2009), including the superior engraftment potential of extraocular derived

satellite cells compared to those from the TA muscle (Stuelsatz et al., 2015), careful consideration needs to be given to other muscle groups.

The most commonly used acute injury models involve intramuscular injection of myotoxins (Cardiotoxin (CTX) and Notexin (NTX)), Barium chloride ( $\text{BaCl}_2$ ), and mechanical injury (freeze, needle or crush injuries) (Gayraud-Morel et al., 2009; Hardy et al., 2016) (**Figure 1**). Myotoxins diffuse readily within muscle and allow a homogenous myofibre regeneration throughout. However, the reproducibility of injury is limited by batch variability of toxin and satellite cell survival following their administration (Gayraud-Morel et al., 2007; Hardy et al., 2016). Of note, NTX also has a neurotoxic effect by blocking acetylcholine release thereby altering the neuromuscular junction (NMJ) thus full muscle repair requires NMJ restoration as well. In addition, NTX injury induces calcium deposits and persistent macrophage infiltration detectable up to three months post-injury.

$\text{BaCl}_2$  does not suffer from batch variations and it induces uniform neofibre formation. However, a single injection often leaves non-injured zones within the tissue; thus, several injections of small volumes need to be performed. These chemical methods can provoke satellite cell loss up to 80%, and this can vary according to severity of injury.

By contrast, freeze-injury by direct contact of a liquid nitrogen pre-cooled metallic rod with the muscle is the most severe, provoking satellite cell loss of up to 90% depending on the number of freeze-thaw cycles administered. This cryolesion induces an acute necrosis giving rise to a “dead zone”, devoid of viable cells, and a distal spared zone that constitutes the cellular source for regeneration. This directional recovery is convenient in some cases to study directional migration and infiltration of the different populations within the tissue. In contrast to toxins or  $\text{BaCl}_2$  treatment, freeze-injury also destroys vasculature.

Transient or permanent denervation can be performed generally by sectioning the sciatic nerve of the mouse leg (**Figure 1**, double dashed lines). Denervation results in progressive degeneration characterized by an atrophy of the muscle and significant fibrosis. This model is suitable to study muscle fibre type specificity (fast vs slow) and the role of electrical stimulation of the muscle fibres by the nerve.

Notably, in some cases, a single round of injury is not sufficient to reveal a significant phenotype, whereas multiple rounds of injury can provoke dramatic phenotypes for both wild type and mutant muscles (Kitamoto and Hanaoka, 2010; Martinet et al., 2016; Urciuolo et al.,

2013).

Models of chronic degeneration/regeneration are also available to study muscle repair in a pathological context. The most broadly used model is *Mdx*, an X-linked muscular dystrophy with nonsense mutation in exon 23 of dystrophin, a critical membrane protein connecting the extracellular matrix with cytoskeleton (Sicinski et al., 1989). Despite being deficient for dystrophin, *Mdx* mice do not suffer from the severe clinical symptoms found in human DMD patients (Chamberlain et al., 2007). Nevertheless, skeletal muscles in *Mdx* mice undergo repeated bouts of degeneration and regeneration thereby providing an excellent model to investigate stem and stromal cell dynamics and inflammation without external intervention. Intriguingly, satellite cells deficient for syndecan-3 (*Sdc3*<sup>-/-</sup>), a cell-adhesion regulator, fail to replenish the pool of quiescent MuSCs upon injury (Pisconti et al., 2010); however, in the *Mdx* mouse, the loss of *Sdc3* increases the pool of proliferating myoblasts (*Myf5*<sup>+</sup>/*Pax7*) resulting in enhanced muscle regeneration and function (Pisconti et al., 2016). *Mdx* mice also provide an important model to study MuSC heterogeneity in different muscle groups, where inaccessible muscles such as the extraocular, which are spared in human (Kaminski et al., 1992), can be investigated.

Skeletal muscle injuries resulting from direct trauma (contusions), partial tears, fatigue, following surgical procedures or myopathies are common and present a challenge in traumatology, as therapy and recuperation are not well supported. After trauma, the regeneration process involves the participation of diverse cell types that modulate their behaviours according to secreted and biomechanical cues. Although MuSC engraftment following transplantation has shown successful partial repair, their low survival and self-renewal capacities, and inability to diffuse in the tissue, remain a brake for cellular therapy. Interestingly, the combination of stem cells, growth factors and bioengineered scaffolds was shown to enhance the regenerative capacity of transplanted MuSCs, therefore opening new avenues of research (Rossi et al., 2011; Sadtler et al., 2016) (**Figure 1**).

### **Cellular regulators of muscle repair and their regenerative potential**

Skeletal muscle regeneration follows three distinguishable and overlapping phases. The first phase of degeneration following severe injury is characterized by necrosis and significant

inflammation. After clearance of cellular debris, new fibres form and transiently express embryonic and neonatal Myosin Heavy Chain (MyHC) from 3-14 dpi. The remodelling phase is characterized by hyperplasia and hypertrophy regulated in part by the IGF-1/Akt and TGF $\beta$ /Smad pathways. IGF-1 affects the balance between protein synthesis and protein degradation thus inducing muscle hypertrophy, whereas TGF $\beta$  negatively controls muscle growth (Schiaffino et al., 2013). Interestingly, recent studies demonstrated a new role for the TGF $\beta$ /Smad pathway in satellite cell expansion (Paris et al., 2016) and differentiation (Rossi et al., 2016). During the final steps of muscle remodelling the vasculature and innervation patterns are restored and new MuSCs are set aside.

MuSCs are located between the basement membrane containing a basal lamina, and the plasmalemma of the muscle fibre (Mauro, 1961). MuSCs are quiescent ( $G_0$  phase) during homeostasis (Rumman et al., 2015; Schultz et al., 1978). Following injury, they re-enter the cell cycle, proliferate to give rise to myoblasts that differentiate and fuse to restore the damaged fibre or generate myofibres *de novo* (Moss and Leblond, 1970; Reznik, 1969; Snow, 1977). During this process, a subpopulation of myogenic cells is set aside for self-renewal (Collins et al., 2005; Motohashi and Asakura, 2014; Relaix and Zammit, 2012). Once activated, MuSCs generate myoblast that differentiate, or self-renewal (**Figure 2**) while undergoing symmetric (SCD) or asymmetric (ACD) cell divisions (Kuang et al., 2007; Rocheteau et al., 2012). How and when these decisions are regulated on a population level remains obscure.

Although satellite cells play a crucial role in restoring myofibres following injury, it is clear that other cells types impact on the regeneration process (**Figure 2**). For example, fibro-adipogenic progenitors (FAPs) reside in the muscle interstitium, express the surface markers PDGFR $\alpha$  (platelet-derived growth factor receptor), Sca1 (stem cell antigen 1) and CD34, and are able to differentiate into fibroblasts and/or adipocytes (Joe et al., 2010; Uezumi et al., 2010). Following acute injury, FAPs activate and amplify, some are eliminated by apoptosis induced by pro-inflammatory cytokines such as IL4 (Joe et al., 2010). Coculture experiments demonstrated that FAPs represent a transient source of pro-differentiation factors for driving proliferating myoblast differentiation and fusion; and it has been shown that pharmacological inhibition of FAP proliferation and differentiation, or diphtheria toxin ablation of these cells results in impaired muscle regeneration (Fiore et al., 2016; Murphy et al., 2011). On the other hand, during chronic degeneration/regeneration, FAPs are the main source of fibrosis, and in

dystrophic mice, the combination of a pro- and anti-inflammatory secretome (Villalta et al., 2009) maintains FAPs survival and differentiation into matrix-producing cells similar to fibroblasts (Lemos et al., 2015). Thus, FAPs play a significant myogenic and trophic role in muscle physiology during regeneration.

Regeneration can also involve fusion of non-resident blood-derived cells to myofibres, however this occurs at too low a frequency to be considered as a viable therapeutic strategy (Ferrari et al., 1998). Pericytes are located peripheral to the endothelium of microvessels and are involved in blood vessel growth, remodelling, homeostasis, and permeability (Armulik et al., 2011). Pericytes in skeletal muscles are constituents of the satellite cell niche where they secrete molecules such as IGF1 (insulin growth factor-1) or ANGPT1 (angiopoetin-1) to modulate their behaviour but also postnatal myofibres growth and satellite cell entry in quiescence (Kostallari et al., 2015). After muscle injury, pericytes activate and give rise to a subset of vessel-associated progenitors called mesoangioblasts when isolated from the tissue. Originally isolated from the embryonic dorsal aorta, pericytes and mesoangioblasts of skeletal muscle were found to express similar markers (Dellavalle et al., 2011; Dellavalle et al., 2007; Kostallari et al., 2015). Mesoangioblasts have a lower myogenic potential compared to MuSCs however, they expand, migrate and extravasate upon arterial delivery in dystrophic murine and canine models, resulting in increased engraftment efficiency and improved muscle function (Berry et al., 2007; Diaz-Manera et al., 2010; Sampaolesi et al., 2006).

In addition to these cell populations, mesenchymal cells that express the transcription factor Twist2 were recently reported to act as myogenic progenitors, however, with selective type IIb fibre-differentiation potential (Liu et al., 2017). PICs (Pw1+ Interstitial Cells) were also reported to engraft efficiently and contribute to myofibre regeneration following intramuscular injection (Mitchell et al., 2010). The imprinted stem response gene Pw1 is expressed in satellite cells, as well as a subset of interstitial cells, however, the relationship between PICs, FAPs, mesoangioblasts and Twist2+ cells remains unclear (**Figure 2**). Mesenchymal "stem" cells (MSCs) have been isolated from virtually all tissues and organs, however, the lack of specific markers has made their characterisation challenging, particularly in light of a recent report showing that mesenchymal stromal cells from different tissues have different transcriptome profiles and differentiation potentials (Sacchetti et al., 2016). Given the advanced state of analysis interstitial cells in muscle, it would be important to establish their lineage relationships and myogenic potential, and define more clearly general features of

MSCs. Recent technological advancements in single cell mass cytometry now permit investigations of cellular heterogeneity within specific cell populations (Spitzer and Nolan, 2016). This technique based on a combination of markers conjugated to metal isotopes led to the identification and classification of subpopulations of myogenic cells following muscle injury (Porpiglia et al., 2017), and it can be used to assess the relative potential and role of myogenic as well as stromal cells at the single cell level.

As indicated above, muscle homeostasis and regeneration involve the interplay of numerous cell types. Inflammatory resident and infiltrating cells also play important roles. Neutrophils/monocytes are the first cells to be recruited following tissue damage, as they appear within 3h following injury and they are no longer detectable after 3 days (Chazaud et al., 2003; Tidball and Villalta, 2010). Their action on the necrotic tissue relies on proteolysis, oxidation and phagocytosis. Muscle-specific inhibition of neutrophil/monocyte activation results in a delay in regeneration upon acute injury (Nguyen et al., 2005).

Macrophages play a critical role during the initial stages following tissue damage as they are required for phagocytosis and cytokine release. The first wave of macrophages (peak at 3 days) promotes myoblast proliferation via the secretion of pro-inflammatory molecules such as TNF $\alpha$  (Tumor Necrosis Factor  $\alpha$ ), INF $\alpha$  (Interferon  $\alpha$ ) or IL6 (Interleukin 6) (Lu et al., 2011). Subsequently, macrophages undergo a phenotypical and functional switch toward an anti-inflammatory fate characterized by the production of IL4 or IL10, for example (Arnold et al., 2007). As mentioned above, this anti-inflammatory response stimulates FAPs, mesoangioblasts, and also directly myoblasts to promote differentiation and fusion (Chazaud et al., 2003; Saclier et al., 2013). Importantly, muscle-resident macrophages are also involved in the immune response following injury (Brigitte et al., 2010; Juban and Chazaud, 2017) yet the cellular source of the homeostatic recovery of the resident macrophage population upon damage in adult mice is still lacking. Notably, two distinct embryonic origins of macrophages have been reported: those arising from haematopoietic stem cells (HSCs), and resident macrophages that are found in all tissues and that are derived from the yolk sac (Gomez Perdiguero et al., 2015). Interestingly, upon acute lung injury, inflammatory macrophages undergo apoptosis while the resident cells persist (Janssen et al., 2011). However, resident macrophages could also arise from bone marrow-derived macrophages undergoing phenotypic conversion to become tissue-resident macrophages (Davies et al., 2013; Yona et

al., 2013). It would be important to determine the relative roles and dynamics of yolk sac and HSC-derived macrophages in homeostasis and regeneration (**Figure 2**).

Muscle vascularisation and angiogenesis provide structural, cellular and molecular support during homeostasis, regeneration and adaptation. The importance of microvessels in the composition of the stem cell niche is highlighted by the tight proximity (within 21 $\mu$ m) of  $\approx$ 90% of MuSCs with vessels (Christov et al., 2007). The number of MuSCs and capillaries, as well as the timing of angiogenesis and myogenesis, are orchestrated during regeneration suggesting a reciprocal interaction between these cell types (Luque et al., 1995). Co-culture experiments revealed that endothelial cells stimulate growth of satellite cells through the secretion of variety of growth factors including IGF-1 (insulin growth factor 1), VEGF (vascular endothelial growth factor), HGF (hepatocyte growth factor), PDGF-BB (platelet-derived growth factor) and FGF (fibroblast growth factor) (Christov et al., 2007). Furthermore, adenoviral overexpression of VEGF *in vivo*, combined with IGF treatment, resulted in increased satellite cell proliferation (Arsic et al., 2004). In a reciprocal manner, differentiating myoblasts, through VEGF, also stimulate angiogenesis (Chazaud et al., 2003; Christov et al., 2007; Rhoads et al., 2009). In addition, several other factors such as MCP-1 (monocyte chemotactic protein), ANGPT2, NGF (nerve growth factor) synthesized by endothelial cells at the early stages of regeneration can stimulate angiogenesis and thus muscle repair (see (Wagatsuma, 2007)). Finally, periendothelial cells (fibroblasts from the endomysium and smooth muscle cells) stabilise regenerated vessels and are capable of stimulating the self-renewal and re-entry in quiescence of a subset of myoblasts through the action of ANGPT1 (Abou-Khalil et al., 2009; Kostallari et al., 2015).

Adult satellite cells reside in a hypoxic microenvironment (Simon and Keith, 2008) and it has been shown that the lack of oxygen (anoxia) in post-mortem muscles, triggers satellite cells to enter a more quiescent state called dormancy (Latil et al., 2012; Rocheteau et al., 2012). Moreover, purified satellite cells cultured in hypoxia (3% O<sub>2</sub>) showed higher engraftment and self-renewal capacities resulting in enhanced muscle repair (Liu et al., 2012). Consistently, the *in vivo* depletion of HIF1 $\alpha$  and HIF2 $\alpha$  (Hypoxia Inducible Factor), important transcription factors mediating the cellular response to low O<sub>2</sub> level, specifically in satellite cells (*Pax7<sup>CreERT2</sup>; HIF<sup>fllox</sup>*) induces a delay in repair due to a self-renewal impairment and inhibition of Notch signalling (Yang et al., 2017).

It has been proposed that microvascular insufficiency could be responsible for the local inflammation and necrosis observed in both dystrophin-deficient mouse and human (Cazzato, 1968). Among the dystrophin-associated proteins is the nitric oxide synthase (nNOS) that is associated with the sarcolemma, and produces diffusible NO to optimize blood flow by sympathetic vasoconstriction attenuation (Anderson, 2000; Kobayashi et al., 2008). In dystrophic animal models and human, the loss of NO abrogates this protective mechanism and the sustained vasoconstriction induces deleterious ischemia resulting in myofibre lysis (Kobayashi et al., 2008; Thomas et al., 1998). Thus, pharmacological restoration of NO downstream signalling to increase blood flow had been proposed, for example, by the use of phosphodiesterase 5A (PDE5A) inhibitors to increase the cGMP downstream effector of NO (Malik et al., 2012; Martin et al., 2012). In *Mdx* mice, PDE5A inhibition was reported to improve muscle ischemia, reduce muscle injury and fatigue (Kobayashi et al., 2008). Clinical trials with encouraging alleviation of microvascular ischemia and restoration of blood flow were reported in the majority of patients tested (Martin et al., 2012).

In summary, regenerative myogenesis involves the interplay of multiple cell types. The identification of subpopulations of mesenchymal stromal cells with different properties provides impetus to characterise in detail their respective roles in the regeneration process. It is not clear to what extent these stromal cell populations are present, and if they play similar roles in regeneration in other tissues, and in other organisms.

### **Strategies for muscle regeneration in different organisms**

The process of regeneration is common in metazoans, from cnidarians such as *Hydra* to higher vertebrates, although their regenerative capacities vary widely. Some metazoans such as planarian or annelid worms can rebuild entire body parts when cut into segments, whereas vertebrates like salamanders can regenerate lens, retina, heart, CNS and can regrow fully functional appendages after amputation. In contrast, mammals fail to regenerate missing body portions, but they can repair injured skeletal muscles, peripheral nervous system or liver with reasonable efficiency (Carlson, 2005; Gurtner et al., 2008).

Interestingly, muscle regeneration constitutes a unique evolutionary conserved phenomenon among bilaterians, as it has been described in arthropods, planarian and annelid worms, ascidians, fish, amphibians (salamander, xenopus) and mammals (mouse, pig, bovine). However, the strategies and the cellular dynamics regulating muscle regeneration can be



markedly distinct among species. To date, two main mechanisms have emerged for the origin of regenerated muscle: myofibre dedifferentiation, or the contribution of Satellite-Like Cells (SLCs), similar to satellite cells identified in other vertebrates (**Figure 3**).

In *Xenopus*, the muscle repair process is studied by amputation of the tadpole tail which is composed mainly of striated muscle. Amputation induces the formation of a blastema, a mesenchymal structure composed of highly proliferative progenitors cells that will differentiate further and form a new functional limb (Straube and Tanaka, 2006). The regeneration of *Xenopus* muscle relies on the amplification of a Pax7+ myogenic cells in the blastema (Chen et al., 2006) rather than de-differentiation, as the fibres near the amputation site simply undergo cell death (Gargioli and Slack, 2004). Following ablation of the Pax7+ SLC population, the tail can still regenerate, but it contains little or no muscle (Chen et al., 2006).

The salamander, a urodele amphibian, can regenerate the limbs multiple times, independently of its age (Straube and Tanaka, 2006). Using Cre-lox-based genetic fate mapping of muscle to compare limb repair in two salamander species, it was reported that in the newt (*Notophthalmus virisecens*), muscle regeneration relies mainly on fibres that de-differentiate into Pax7-negative proliferative mononucleated cells that further generate new myofibres (Sandoval-Guzman et al., 2014) whereas the larvae uses SLCs (Tanaka et al., 2016). In contrast, in the neotenic axolotl (*Ambystoma mexicanum*), myofibres do not contribute to muscle regeneration while grafting experiments showed the recruitment of Pax7-positive SLCs that proliferate in the blastema and regenerate new fibres (Sandoval-Guzman et al., 2014). These unexpected findings reveal that distinct muscle regeneration strategies appear to have evolved among these salamanders that are 100 million years apart (Steinfartz et al., 2007).

Similarly to mammals and amphibians, the presence of adult SLCs has been described in several fish species including salmon, carp, and electric fish (Weber et al., 2012). In zebrafish larvae, muscle injury by puncture wounds to the ventral myotome induces proliferation of SLCs, differentiation and fusion to repair damaged myofibres (Knappe et al., 2015). Of note, the *Pax7* gene is duplicated in zebrafish (*Pax7a* and *Pax7b*), and they differ in expression pattern and function: *Pax7a*-cells participate in repair of the first wave of nascent fibres whereas *Pax7b*-cells generate larger fibres (Pipalia et al., 2016). The ablation of one population or the other results in deficits in repair suggesting lack of compensation (Pipalia et

al., 2016). Similarly, it has been shown in the adult electric fish (*S. macrurus*) that muscle repair following tail amputation also involves Pax7-positive SLCs, but not myofibre dedifferentiation (Weber et al., 2012). Interestingly, according to the muscle type, the zebrafish is capable of exploiting both strategies: extraocular muscle injury using partial myectomy of the lateral rectus showed no SLC contribution to muscle regeneration, instead, residual myocytes undergo dedifferentiation (Saera-Vila et al., 2015).

Recently, other chordate models emerged to study the evolution of regenerative biology at the invertebrate-vertebrate transition. The basal chordate amphioxus shows a high regenerative potential and it is capable of regrowing both anterior and posterior structures during adult life, including neural tube, notochord, fin, and muscle after amputation (Somorjai et al., 2012). Interestingly, amphioxus possesses peripheral Pax3/7+ cells present in the embryo and located under the basal lamina in adult resting muscle. These cells amplify upon amputation migrate toward the periphery of degrading myofibres and fuse. These and other studies suggest that amphioxus is a tractable model for regenerative myogenesis, and it has extensive regenerative capacities beyond those of more complex vertebrates (Somorjai et al., 2012).

As another example, the crustacean *Parhyale hawaiiensis* develops a blastema structure after thoracic leg amputation followed by extensive growth of the limb and generation of a new musculature later after moulting (Konstantinides and Averof, 2014). Moreover, Pax3/7-expressing cells of mesodermal origin are tightly associated with mature *Parhyale* muscles and transplantation experiments of labelled SLCs in wild-type individuals have shown that muscle regeneration is based on SLCs as observed in vertebrates (Konstantinides and Averof, 2014).

In contrast, pre-bilaterian animals such as cnidarians possess muscles formed by epitheliomuscular cells that can be striated (*Medusa*) or not (*Hydra*) (Leclere and Rottinger, 2016). Although regeneration in cnidarians has been reported (Leclere and Rottinger, 2016), limited data is available on the cellular origin of muscle repair. After wounding, the striated muscle in jellyfish dedifferentiates into non-proliferating mononucleated cells that migrate toward the site of injury before undergoing differentiation (Lin et al., 2000).

The studies performed in diverse chordate species, arthropods and cnidarians suggest that the cellular basis of regeneration implicating Pax3/7-positive SLCs was present in the common ancestor of bilaterians (**Figure 3**). The different strategies employed for muscle repair, even

in evolutionary related species, highlights the highly conserved regulation of the regeneration process, and it points to satellite cells as an ancient evolutionary stem cell type present throughout bilaterian phylogeny (**Figure 3**). However, the relative role of interstitial cells in regenerative myogenesis is less well understood in non-murine models. Furthermore, understanding the loss of regenerative capacity in human has been the topic of intense debate for decades thereby prompting more detailed investigations of animal models with superior regenerative capacity. One hypothesis proposes that suppression of dedifferentiation and cell cycle reentry were lost in mammals in favour of a tumour suppression program to prevent carcinogenesis. For example, the *in vitro* inhibition of two tumour suppressor proteins (ARF and Rb) in mouse primary muscle cells induce myotubes to reenter the cell cycle (Pajcini et al., 2010). Similarly, inhibition of the p53 tumour suppressor in newt primary myotubes triggers their fragmentation into mononucleated cells that reenter cell cycle (Wang et al., 2015). In addition, the knock-down of p16<sup>INK4</sup>, another potent tumour suppressor that accumulates in aged individuals, leads to an extensive increase in regenerative potential of pancreatic islets (Krishnamurthy et al., 2006). However, whether those tumour suppressors are inhibited in the fish and amniotes requires investigations to support the cancer hypothesis. It would be interesting to explore the status of tumour suppressors using two structures that differ by their repair mechanism: such as the zebrafish extraocular muscle (dedifferentiation, (Saera-Vila et al., 2015)) versus the tail (SLCs).

## Conclusion

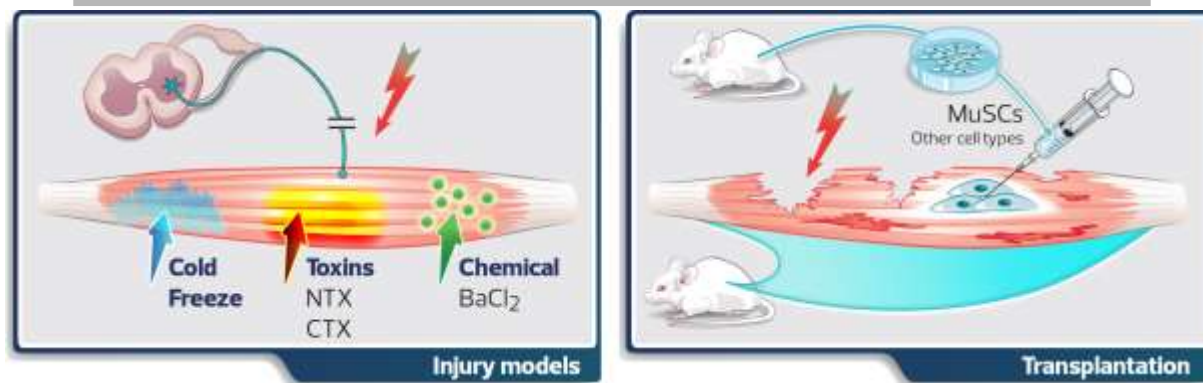
Skeletal muscle has been used for decades to study regenerative medicine and stem cell biology, however, the field still lacks a standard injury and repair protocol allowing comparisons between laboratories. Although by 28 days post-injury the muscle is considered to be largely regenerated, the timing of regeneration can be different from one injury model to another: eg, new vessels are formed 2dpi after chemicals injuries while this event takes up to 12 days following freeze-injury (Hardy et al., 2016). Another area that requires detailed investigation is the study and characterisation of interstitial stromal cells. The identification of "mesenchymal stem cells" in tissues has generated some confusion as this population exhibits considerable heterogeneity. The identification of several stromal populations in skeletal muscle can be used as a starting point to isolate cells with potentially similar properties in other tissues with the aim to define stem-stromal interactions in niches of different tissues and organs. Finally, the inability to regenerate a whole appendage in mammals remains puzzling, although intriguingly, heart and digit tip regeneration have been reported to occur during early

perinatal growth under certain conditions, but these capabilities are lost within days (Seifert et al., 2012). Detailed investigations on comparative evolutionary biology of organisms that have retained and lost regenerative capacity will allow us to identify the underlying mechanisms responsible for this fascinating phenomenon.

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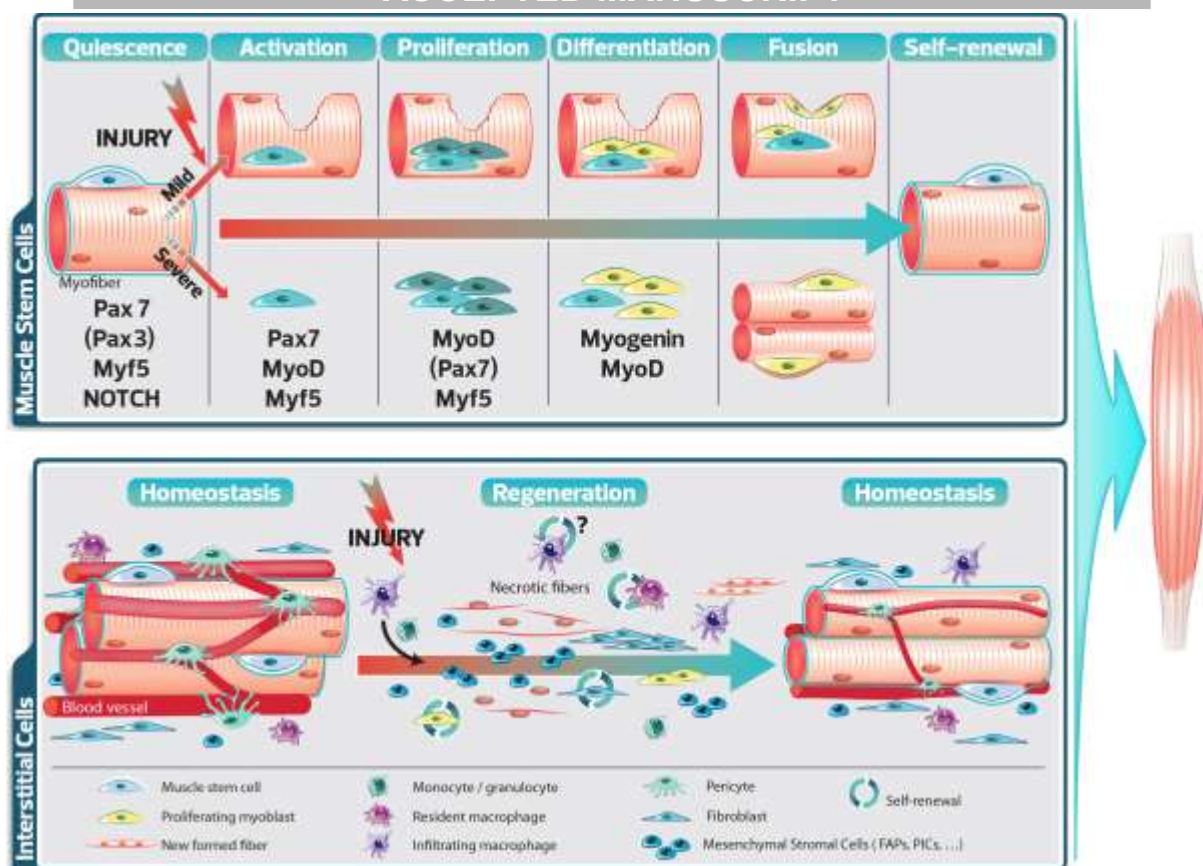
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Accepted manuscript



**Figure 1. Schematic representation of endogenous and transplanted cells during muscle regeneration.**

Left: CTX and NTX permeabilise or hydrolyse lipids on the myofibre membrane, respectively, resulting in myofibre degradation (Chang et al., 1972; Gutierrez and Ownby, 2003). Cardiotoxin (CTX, protein kinase C inhibitor) and Notexin (NTX, phospholipaseA2) are isolated from snake venom, and they trigger an increase in  $\text{Ca}^{2+}$  influx followed by fibre depolarization and consequently myofibre hypercontraction and necrosis. Chemical injury can be induced by using barium chloride ( $\text{BaCl}_2$ ), a divalent alkaline earth metal that inhibits the  $\text{Ca}^{2+}$  efflux in the mitochondria in addition to stimulation of exocytosis by its barium ions. Right: Transplantation is generally performed using isolated Muscle Stem Cells (MuSCs). However, other cells types such as Fibro-Adipogenic Precursors (FAPs), Pw1 Interstitial Cells (PICs) and mesoangioblasts have been transplanted in different contexts.



**Figure 2. Synoptic view of the different cell populations involved in muscle repair.**

Top: Following mild or severe injury, quiescent muscle stem cells (MuSCs) activate, differentiate and fuse to repair the damaged fibre. Mild injury induces fibre break and recruitment of surrounding satellite cells on the intact part of the fibre. In contrast, severe injury triggers complete myofibre destruction followed by satellite cell proliferation and differentiation on extracellular matrix remnants referred to as “ghost fibres”(Webster et al., 2016). Mild and severe injuries activate a tightly regulated myogenic process including interplay of key transcription factors. During homeostasis, satellite cells are quiescent and express *Pax7* (and *Pax3* in some muscles) and *Myf5*, and Notch signalling is highly active. Upon damage, they rapidly upregulate *Myod* and *Myf5*, and *Pax7* protein remains detectable. Following the amplification phase, myoblasts express the terminal differentiation gene *Myogenin* and exit the cell cycle. Differentiated myoblasts fuse to the pre-existing fibre (mild) or together to form new fibres (severe). During this process, some satellite cells self-renew to replenish the stem cell pool.

Bottom: Although the generation of new fibres is dependent on MuSCs, other cell types such as macrophages, monocytes, mesenchymal stromal cells (including FAPs, mesoangioblasts and PICs), pericytes and fibroblasts are also critical for the regeneration process.

		Type of wound	Cellular contribution	Reference		
Pre-bilaterians	<b>Cnidarians</b> Jellyfish	Scrapping off small part of swimming muscle	MDD	Lin, 2000		
	Bilaterians	<b>Arthropods</b> Parhyale	Limb amputation	SLCs	Konstantimides, 2014	
<b>Cephalochordates</b> Amphioxus		Tail amputation	SLCs	Somorjai, 2012		
<b>Fish</b> Electric fish Zebrafish *		Tail amputation	SLCs	Weber, 2012		
		Puncture larvae ventral myotome	SLCs * MDD in EOM	Knappe, 2015 Saera-Vila, 2015		
Vertebrates		<b>Amphibians</b> Xenopus Axolotl Newt	Tadpole tail amputation Limb amputation Limb amputation	SLCs SLCs MDD adult SLCs in larvae	Chen, 2016 Sandoval-Guzman, 2014 Sandoval-Guzman, 2014 Tanaka, 2016	
		Amniotes	<b>Mammals</b> Mouse Human	Toxins, chemicals, mechanical, Eccentric exercise	MuSCs MuSCs	Sambasivan, 2011 Whitehead, 1998

**Figure 3. Muscle regenerative ability of pre-bilaterians and bilaterians.**

MDD: Myofibre dedifferentiation, SLCs: Satellite-Like Cells, MuSCs: Muscle Stem Cells.

\* MDD contributes to zebrafish adult extraocular muscle (EOM) regeneration. Note that the newt regenerates muscle using MDD in the adult and SLCs in the larvae.

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### Highlights:

- . Some animals can regenerate injured structures while others cannot
- . Different species have evolved unique strategies to regenerate structures
- . The role of muscle stromal cells is actively being explored in regeneration
- . Various injury models are used each with unique outcomes on muscle regeneration