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*Review article*

# Contribution of stem cells to skeletal muscle regeneration

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**Abstract:** Stem cells for skeletal muscle originate from dermomyotome of the embryo. The early marker of these cells is expression of both transcription factors *Pax3* and *Pax7* (*Pax3+/Pax7+* cells). The skeletal muscles in the adult organism have a remarkable ability to regenerate. Skeletal muscle damage induces degenerative phase, followed by activation of inflammatory and satellite cells. The satellite cells are quiescent myogenic precursor cells located between the basal membrane and the sarcolemma of myofiber and they are characterized by *Pax7* expression. Activation of the satellite cells is regulated by muscle growth and chemokines. Apart from the satellite cells, a population of adult stem cells (muscle side population - mSP) exists in the skeletal muscles. Moreover, the cells trafficking from different tissues may be involved in the regeneration of damaged muscle. Trafficking of cells in the process of damaged muscle regeneration may be traced in the SCID mice. (www.cm-uj.krakow.pl/FHC)

**Key words:** Skeletal muscle - Regeneration - Stem cells - Satellite cells - SCID mice

## Origin of stem cells for skeletal muscle

Problems concerning the origin of skeletal muscle progenitor cells were recently presented by Gros *et al.* [25] and Relaix *et al.* [47]. During early embryonic development, mesodermal cells of somite undergo specialization to sclerotome and dermomyotome for skeletal muscle and skin, respectively. The authors used cell labeling with green fluorescent protein (GFP) and grafting experiments to follow trafficking of muscle progenitor cells during embryogenesis. The skeletal muscle progenitor cells move from central dermomyotome region and undergo differentiation to mesenchymal cells. At this early embryonic stage skeletal muscle-specific markers cannot be detected. Later, most of the skeletal muscle progenitors express molecular markers *Pax7* and *Pax3* (*Pax3+/Pax7+* cells). The *Pax* genes encode evolutionarily conserved transcription factors that play critical roles in the development [46]. These molecular markers characterize satellite cells (*Pax7*) and myoblasts (*Pax3*), respectively. The *Pax3+/Pax7+* cells are maintained as a proliferating population in embryonic and fetal muscles and constitute muscle progenitor cells in the embryo and fetus. At the end of fetal period, *Pax7*-positive cells appear at satellite cell position in the muscles, while myoblasts represent a distinct cell population [18, 51, 57].

As mentioned, *Pax7+* cells are the satellite cells. The proliferation and differentiation of these precursor cells is observed during growth and repair of the muscles. Moreover, the population of adult stem cells (muscle side population - mSP) is committed to myogenic differentiation *in vivo* and *in vitro* when cocultured with myoblasts [11]. Recently it has also been demonstrated that different circulating progenitors can participate in muscle regeneration (bone marrow-derived cells: c-kit+ myelomonocytic precursors, CD45-/Sca- cells, CD45+/Sca+ cells (reviewed in [40]).

## The damage and repair of skeletal muscle

The adult skeletal muscle turnover is slow, as estimated by BrDU, no more than 1-2% of myonuclei are replaced every week in the rat [49]. However, this stable state of the skeletal muscle rapidly changes after mechanical damage. The muscle regeneration is characterized by

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two phases: degeneration (necrosis) and reconstruction. Whether the muscle injury is induced by direct trauma, extensive physical activity or innate genetic defects, the degeneration process is characterized by the damage of the myofiber sarcolemma resulting in increased myofiber permeability. This may be observed directly by uptake of low-molecular weight dyes such as Evans Blue by myofibers [27]. It has been hypothesized that the change in sarcolemma permeability and calcium influx into the damaged myofibers activates calcium-dependent, non-lysosomal muscle proteases like calpain [3]. The activated calpains may further damage the sarcolemmal and cytoplasmic proteins of the myofibers, and their fragments may then be released from the cell [55, 56]. It is well known that the degenerative phase in the skeletal muscle may be traced by observation of increased serum levels of muscle proteins such as creatine kinase and myosin heavy chain, the proteins usually restricted to the myofiber cytoplasm [54].

Another process in the degenerative phase of the skeletal muscle damage is the accompanying infiltration of this region by leukocytes [38]. The earliest infiltrating inflammatory cells are polymorphonuclear leukocytes followed by monocytes and macrophages. Significant numbers of neutrophils were observed already during the first hours after muscle damage and it was suggested that they play a critical role in phagocytosis and elimination of bacteria and damaged cells [60]. They may also release hydrolytic enzymes stored in their granules and can promote the recruitment and activation of further monocytes/macrophages. The myeloid cell populations recruited may influence the muscle cell death, as observed *in vitro.* Neutrophils can also lyse muscle cells via superoxide-dependent mechanisms [43].

**Table 1.** Expression of molecular markers in quiescent and activated satellite cells in adult skeletal muscle (after [28], modified)

| Molecular marker | Expression in | Reference |
|---|---|---|
| MNF | Q, Ac | [22] |
| Pax7 | Q, Ac | [51] |
| c-Met | Q, Ac | [6, 15, 41, 58] |
| N-CAM | Q, Ac | [16] |
| Syndecan-4 | Q, Ac | [15] |
| Myf5 | Ac | [14] |
| MyoD | Ac | [14] |

Q - quiescent, Ac - activated satellite cells; MNF - myocyte nuclear factor; N-CAM - neural cell adhesion molecule; c-Met - hepatocyte growth factor receptor; Pax7, Myf5, MyoD - transcription factors

**Table 2.** Gene expression sequence in satellite cells during activation and during angiogenesis in muscle regeneration

| State of satellite cells (SC) or endothelial cells (EC) | Transcription factor expression in SC [14] | Gene expression in EC [50] |
|---|---|---|
| Quiescence (M-kadherin+; CD34+ cells) | *Myf5+;* *MyoD* low | CD34, VE-kadherin, von Willebrand factor |
| Activation | *Myf5+;* *MyoD*+; *Myf5MyoD*+ | Hypoxia-inducible factor-1 (HIF-1) |
| Proliferation | *Myf5+;* *MyoD*+; *Myf5MyoD*+ | Hypoxia-responsive genes e.g.: VEGF; iNOS |
| Differentiation; fusion to myotubes | *Myf5MyoD*+; *MyoD*+ | Final result - angiogenesis genes |

## The satellite cells in muscle repair

The cells active in muscle regeneration process are satellite cells [9, 14, 28, 42]. They are self-sufficient as a source for regeneration [11, 13]. Moreover, the satellite cells self-renew, expanding in number and repopulating the muscle with new satellite cells [62]. Neonatal skeletal muscle contains abundant satellite cells as compared with older muscles. Young animal muscle contains more than 30% of satellite cells while about 5% of satellite cells may be found in older animal muscle [23]. Besides the changes of satellite cell number, it has been suggested that increasing age of animal is associated with a reduced proliferative capacity of satellite cells.

The satellite cells become activated upon mechanical damage of the muscle or in response to exercise [30]. They enter the cell cycle and proliferate, contributing to myofiber rebuilding and to new satellite cell formation as mentioned above. Parallel revascularization of the damaged region is observed. The satellite cell markers allow their localization in the muscle and *in vitro* after isolation [15, 28] (Table 1). The cells express myocyte nuclear factor MNF, as well as c-met tyrosine kinase receptor (HGF receptor) [22]. The MyoD and Myf5 markers - transcriptional activators of the myogenic regulatory factor (MRF) family - were found in activated and proliferating cells, while at the same time expression of angiogenesis genes may be observed in the endothelial cells (Table 2).

The growth factors such as basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and hepatocyte growth factor (HGF) have been shown to increase myogenic cell chemotaxis, proliferation and differentiation *in vitro* [1, 39]. Some of them may be produced by macrophages or by non-muscle cells [4]. Their role in muscle repair has been demonstrated *in vivo* by immune neutralization of bFGF, insulin-like growth factor-1 (IGF-1) or transforming growth factor beta1 (TGFbeta1) [37]. These factors on day 4 after injury are acting both on inflammatory cells in the muscle damage area and on endothelial cells that are involved in revas-

cularization. Anti-bFGF antibody significantly reduced the number of capillaries in the zone of damaged muscle. However, the reverse effect was observed after the injection of anti-IGF1 or anti-TGFbeta1, that promoted the regenerating muscle revascularization. The IGF I and II are known to regulate satellite cell proliferation and differentiation [10]. Another important growth factor regulating satellite cell activation and differentiation in regenerating skeletal muscle is HGF [41]. HGF receptor, c-Met is localized to satellite cells and adjacent myofibres.

## Immunodeficient mice as a model to study involvement of stem cells in muscle regeneration

The trafficking of stem cells during regeneration of the damaged tissue may be traced *in vivo, e.g.* after implantation of exogenous human stem cells in the SCID mouse [19, 24]. The *scid* mutation was first described in 1983 in BALB/c C .B-17 strain mice [7, 17]. The SCID mice (Severe Combined ImmunoDeficiency) have normal internal microenvironment for hemopoiesis, and develop mature monocytes, polymorphonuclear leukocytes, megakaryocytes, erythrocytes and NK cells; they also show elevated level of hemolytic complement. However, the mice lack both humoral and cell-mediated immunity due to the absence of mature and functional B and T lymphocytes [17]. Since the specific immunity of SCID mice is damaged, the mice may be used as a convenient small animal model for implantation of human normal or pathological cells/organs. However, in xenotransplant experiments, the mouse NK cells may attack the implanted cells. Convenient method for prolongation of the transplant survival in SCID mouse is treatment of the host animal with chemotherapeutic agents (cyclophosphamide, busulfan) or by irradiation before xenotransplant transfer [2]. The treatment with cytostatics or irradiation, however, damages not only NK-cells, but also cells of several other tissues and organs that may influence the result of experiment. To avoid partly the NK cell activity in the SCID mice a treatment with specific anti-mouse NK-cells antibody (anti-NK1.1) was proposed [33, 34]. Another possibility is the use of the NOD-SCID mice. The NOD mouse is an animal of spontaneous autoimmune T-cell mediated insulin-dependent diabetes [31]. The mice are deficient in NK cells, display defects of myeloid development and function, some animals lack C5 complement protein and cannot generate the hemolytic complement activation. The new mouse strain, NOD/LtSz-*scid* mice was generated by crossing the *scid* mutation from C.B.-17-*scid* mice onto the NOD background. The NOD/LtSz-*scid* mice lack an adaptive immune system, and do not develop diabetes [52]. Their macrophages have reduced ability to secrete IL-1 in response to LPS, and the animal lack hemolytic complement. The mice have the mean life span of only about 8 months due to high incidence of thymic lymphomas. The above described NOD/*scid* mice *in vivo* system may be used to test the possible participation of human stem cells in repair of damaged mouse tissues.

## Stem cell trafficking in mice as possible source of cells in muscle regeneration

The stem cells derived from bone marrow have been considered as candidates for transplantation therapy of muscle degenerative disorders [20]. Furthermore, the stem cells isolated from adult bone marrow, the neuronal compartment and mesenchymal tissues are able to differentiate into the myogenic lineage *in vivo* and *in vitro* [5, 8, 12, 35]. In response to chemokine signals, stem cells become crowded at some sites of the organism, *e.g.* in the bone marrow, and also in skeletal muscles [44]. The migration of muscle progenitor cells is a complex process and requires signals that allow the cells to remain motile and find their target [40]. In the striated muscle, there are at least two systems regulating the cell migration, present during embryonic development and muscle regeneration in the adult organism: HGF ligand and c-Met receptor [6, 29, 41, 53, 58] as well as SDF-1 ligand and CXCR4 receptor [29, 44, 45]. The expression of both ligands: HGF and SDF-1 is predominantly restricted to fibroblasts and stromal cells [53].

The myogenic precursor cells derived from bone marrow may take part in muscle regeneration [20]. The unfractionated mouse bone marrow cells genetically labeled with gene encoding nuclear beta-galactosidase (beta-Gal), were implanted intramuscularly into the damaged muscle of the *scid/bg* mice. The authors observed regenerating myofibers containing beta-Gal nuclei 2 and 3 weeks after the injury. In another experiment, normal, wild-type mouse bone marrow was transplanted into the *mdx* mouse [26]. The *mdx* mouse is a model of Duchenne's muscular dystrophy in humans, and their muscles are devoid of dystrophin expression. In the *mdx* mice muscles with the implanted wild-type bone marrow stem cells, dystrophin expression was observed suggesting that bone marrow stem cells participate in muscle reparation.

The regeneration of tissues after implantation of non-embryonic stem cells creates the possibility of therapy. It has been shown that human umbilical cord blood (HUCB) contains a significant number of stem cells [36, 48]. The HUCB cells are competent in the process of myogenic differentiation *in vitro* [21].These cells injected retro-ocularly were capable of myogenic differentiation in the host muscle and participated in the myofiber reconstruction in *sjl* dystrophic mice [32].

We demonstrated the involvement of HUCB cells implanted directly into the damaged muscle in the SCID mouse muscle regeneration (manuscript submitted). The cells were trafficking into the regenerated SCID mouse skeletal muscle and participated in the regeneration. The presence of myofibers showing the expression of human $\beta_2$-microglobulin was observed, suggesting fusion of human and mouse cells. Moreover, the implanted HUCB cells form human muscle precursor cells residing in the mouse repaired muscle and they are able to translocate and home to the bone marrow, spleen and contralateral muscle.

In the mouse, stromal cells of the bone marrow produce SDF-1 ligand [61] enabling engraftment of human cord blood stem cells in the SCID mouse [59, 61]. The human cord blood stem cells express CXCR4 receptor and when implanted into the mouse they are directed into regions of SDF-1 secretion. Mouse and human SDF-1 differ of only in one aminoacid in the sequence, and functionally they are similar [44]. Human cells in the mouse may be recognized as human-MHC expressing cells, thus the cord stem cells may be used as an indicator of SDF-1 production regions in the host mouse organism.

## Conclusions

Skeletal muscle progenitor cells express *Pax7* and *Pax3*, evolutionarily conserved transcription factors. The myoblasts express *Pax3*, while satellite cells *Pax7*. The muscle damaged mechanically, chemically or by extensive activity regenerates with active participation of satellite cells or stem cells from different sources. The regeneration *in vivo* may be traced in mouse models. The use of xenotransplants provides an insight into the general processes involved in regeneration of the muscle and opens the perspectives of novel therapies.

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