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INVITED REVIEW

Myogenic precursor cells in craniofacial muscles

LK McLoon[1,2], KM Thorstenson[1], A Solomon[3], MP Lewis[3]

[1]*Department of Ophthalmology, University of Minnesota, Minneapolis, MN, USA;* [2]*Department of Neuroscience, University of Minnesota, Minneapolis, MN, USA;* [3]*Division of Biomaterials and Tissue Engineering, UCL Eastman Dental Institute, London, UK*

Craniofacial skeletal muscles (CskM), including the masticatory (MM), extraocular (EOM) and laryngeal muscles (LM), have a number of properties that set them apart from the majority of skeletal muscles (SkM). They have embryological origins that are distinct from musculature elsewhere in the body, they express a number of immature myosin heavy chain isoforms and maintain increased and distinct expression of a number of myogenic growth factors and their receptors from other adult SkMs. Furthermore, it has recently been demonstrated that unlike limb SkM, normal adult EOM and LM retain a population of activated satellite cells, the regenerative cell in adult SkM. In order to maintain this proliferative pool throughout life, CSkM may contain more satellite cells and/or more multipotent precursor cells that may be more resistant to apoptosis than those found in limb muscle. A further exciting question is whether this potentially more active muscle precursor cell population could be utilized not only for SkM repair, but be harnessed for repair or reconstruction of other tissues, such as nervous tissue or bone. This is a highly attractive speculation as the innate regenerative capacity of craniofacial muscles would ensure the donor tissue would not have compromised future function.
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Introduction

Individual myofibres in skeletal muscle (SkM) contain multiple myonuclei each of which controls the cytoplasm and cell membrane in its immediate vicinity. Each myofibre has associated with quiescent cells responsible for repair and regeneration, the satellite cells (Mauro, 1961). These cells respond to muscle injury by proliferating and producing myoblasts, which are responsible for regeneration and repair of injured muscles. Recent evidence suggests that there are actually two populations of mononucleated cells with myogenic potential within SkM. There is a majority population that is stimulated by injury to proliferate rapidly, the satellite cells, and a minority population, myogenic precursor cells, that are slow-cycling and considered to be more multipotent and stem cell-like (Qu *et al*, 1998; Beauchamp *et al*, 2000; Olguin and Olwin, 2004).

The craniofacial skeletal muscles (CSkM) have a number of properties that distinguish them from the majority of SkMs in the body (Thorstenson and McLoon, 2006). It is also true that there are distinct differences within CSkM i.e. between MM, EOM and LM. This is particularly intriguing as although the capacity of CSkM as a whole to undergo functional adaptation is high, it appears that there are differences in regenerative potential (Pavlath *et al*., 1998). This review will attempt to encompass both the similarities and differences between members of the CSkM group and then compare these to non-CSkM.

What evidence supports the hypothesis that there are intrinsic differences between craniofacial and limb skeletal muscle?

Craniofacial skeletal muscles have a number of unique properties compared with limb SkM and have been described as a separate allotype (Porter and Baker, 1996). The CSkM continue to express many molecules normally downregulated in adult limb SkM, including, but not limited to, developmental and neonatal myosin heavy chain isoforms (MyHC; Wieczorek *et al*, 1985; Soussi-Yanicostas *et al*, 1990), and NCAM (McLoon and Wirtschafter, 1996).

There are a number of elegant studies on the genetic control of muscle development that show that the myogenic precursor cells within CSkM are distinct from those in limb muscle. Most of the head muscles arise from preoptic axial and paraxial head mesoderm (Noden, 1983) but the connective tissues are neural crest derived (Noden and Trainor, 2006). Early transcription factors that control early somitic muscle

Correspondence: Dr Mark P Lewis, UCL Eastman Dental Institute, 256 Gray's Inn Road, London WC1X 8LD, UK. E-mail: mark.lewis@ucl.ac.uk
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development are not expressed in the developing CSkM (Hacker and Guthrie, 1998; Mootoosamy and Dietrich, 2002). All the somitic muscle, including limb muscle, which migrates from somites, is Pax3-positive during early myogenesis, but craniofacial muscles are Pax3-negative (Brown *et al*, 2005). Even more revealing are studies of the Pax3 knockout transgenic mouse, where limb muscle does not develop, but the head muscles develop normally (Tajbakhsh *et al*, 1997; Buckingham, 2001). This difference in the early genetic control of development between limb and CSkM also is true for the homeobox factor Lbx1; the somitic and limb muscles express this gene while the head muscles except for the lateral rectus are negative (Birchmeier and Brohmann, 2000; Mootoosamy and Dietrich, 2002). Various signaling factors (e.g. Wnt) have been implicated as negative regulators of myogenesis in developing cranial paraxial mesoderm, distinctly opposite from the positive regulatory role these factors play in trunk mesodermal development (Tzador *et al*, 2003). Recent evidence demonstrates a specific role for Pitx2 in extraocular muscle (EOM) morphogenesis specifically (Diehl *et al*, 2006).

There is also evidence in the literature to support muscle-specific differences in regenerative potential. In a study comparing regeneration in the masseter and limb muscles, for example, differing regenerative capacities were linked to intrinsic differences between the muscle precursor cells in these two muscles (Pavlath *et al*, 1998). The EOM are preferentially spared in patients with Duchenne muscular dystrophy (DMD; Karpati and Carpenter, 1986), and the orbicularis oris, laryngeal (LM) and masticatory (MM) muscles also show less severe alterations in models of DMD (Manolides and Baloyannis, 1981; Kiliaridis and Katsaros, 1998; Muller *et al*, 2001). In contrast, the MM and EOM are more commonly affected in patients with myasthenia gravis (Oda, 1993; Benveniste *et al*, 2005).

Evidence from a number of injury models suggests that the craniofacial muscles have a remarkable ability to survive insult, e.g. ageing, injury, functional denervation and disease. When limb SkMs are injected with local anaesthetics, there is significant muscle necrosis (Benoit and Belt, 1970). The EOM, as well as other craniofacial muscles, are fairly resistant to the myotoxicity of these agents (Porter *et al*, 1988; McLoon and Wirtschafter, 1993). The EOM and LM respond differently to botulinum toxin A (Botox), the neuromuscular paralysis agent, than MM and limb SkM where atrophy develops in the latter (Duchen, 1970; Hassan *et al*, 1995; To *et al*, 2001) but not in the former (Spencer and McNeer, 1987; Shinners *et al*, 2006), despite the rapid functional muscle paralysis observed in all muscles (Dimitrova *et al*, 2002). Injection of Botox in the EOM also results in a significant increase in satellite cell activation and myonuclear addition into individual EOM myofibres, while limb muscle shows only a small and abortive response of satellite cells to this functional denervation (Ugalde *et al*, 2005). Denervation of SkM leads to an abnormal phenotype yet surgical section of the recurrent laryngeal nerve (Shinners *et al*, 2006) leads to a significant increase in LM satellite cell activation, and even after 24 weeks, the muscles appear relatively normal (Shinners *et al*, 2006). This correlates with the ability of the LM to survive and be successfully reinnervated after long periods of denervation (Tucker, 1978).

In addition, there are no 'ageing' disorders of the EOM. While there are constrictive changes that can occur within the orbit because of connective tissue and elasticity alteration of the soft tissue pulley structures (Clark and Demer, 2002), there are no reports of sarcopenia. In fact, in one study of cross-sectional areas of EOM from patients ranging in age from birth to 83 years, the muscle fibres were actually 'thicker' in the muscles from the oldest patients (Muhlendyck, 1979). While the literature on ageing in the masseter muscle is somewhat contradictory, there is evidence that masseter muscle structure and function is relatively constant in ageing F344 rats (Norton *et al*, 2001). It may be that in human patients, it is hard to distinguish changes in the masseter with ageing that are primary, rather than secondary to changes in dentition or other aspects of craniofacial anatomy.

What evidence supports the hypothesis that there are intrinsic dierences between the satellite cells from extraocular and limb skeletal muscle?

It is interesting that both masseter and the EOM have a different embryological origin from limb muscles, with different genetic programmes controlling their development. The application of slow or fast patterns of nerve stimulation to denervated, bupivacaine-injured hindlimb muscle resulted in patterns of myofibre regeneration and demonstrated that there are intrinsically different satellite cell populations within different limb SkMs as well (Kalhovde *et al*, 2005). A recent gene array study examined developing EOM and limb muscle and identified a number of distinctive gene and protein expression signatures during normal development (Porter *et al*, 2006), adding weight to the hypothesis that craniofacial and hindlimb muscles are different allotypes, and the myogenic precursor cells derived from different muscles appear to have intrinsically different properties.

Compelling data from the EOM has lead to the suggestion that myogenic precursor cells from CSkM may be intrinsically different from those in limb SkM. A subpopulation of satellite cells within normal, adult EOM is activated, divides and fuses with apparently normal myofibres (McLoon and Wirtschafter, 2002a,b; McLoon *et al*, 2004). This process is not seen in non-CSkM and appears to continue throughout the functional lifespan of the muscle (up to 82 years old in human EOM; McLoon and Wirtschafter, 2003). Furthermore, after the Botox induced functional denervation described earlier, the rate of satellite cell activation (as demonstrated by MyoD upregulation), is significantly greater than that seen in limb muscles (Ugalde *et al*, 2005). Data from the MM is far less available so remains less known.

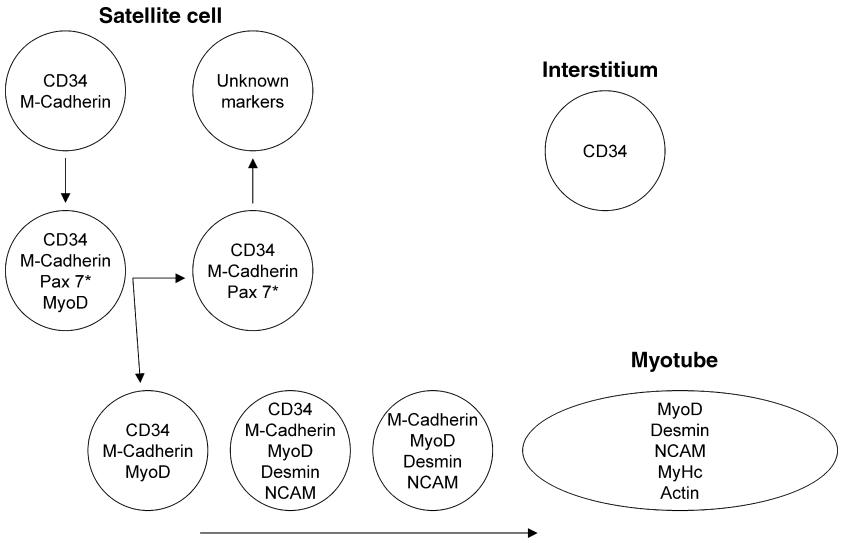

Figure 1 Diagram outlining dynamics of key cellular markers during differentiation between satellite cells and myotubes

How can we accurately define and quantify the satellite cell population in craniofacial and limb muscles?

Satellite cells reside under the basal lamina and are responsible for muscle repair and regeneration in adult animals (Mauro, 1961). The identification of satellite cells both *in vitro* and *in vivo* is complicated by the fact that a wide number of proteins have been described for their identification. In addition, these molecules are known to change with state of activation (e.g. HGF and cMet: Tatsumi *et al*, 1998; MyoD: Olguin and Olwin, 2004). Quiescent satellite cells have been identified by expression of a number of proteins with a wide variety of cellular functions; these include Pax7 (Seale *et al*, 2000; McLoon *et al*, 2004), CD34 (Beauchamp *et al*, 2000), cMet (Allen *et al*, 1995; Cornelison and Wold, 1997), notch (Conboy and Rando, 2002) and m-cadherin (Beauchamp *et al*, 2000). From these studies, it is clear that there are a number of markers available to identify quiescent satellite cells. It is unclear, however, whether they all identify the same cell population.

When the satellite cells are activated, they express additional molecules that can be used for their identification, including HGF (Tatsumi *et al*, 1998), NCAM (Kadi *et al*, 2004a) and various myogenic regulatory factors including MyoD (Montarras *et al*, 1991; Grounds *et al*, 1992), myogenin (Grounds *et al*, 1992) and myf5 (Beauchamp *et al*, 2000; Figure 1). Using multiple markers, we have shown that normal adult EOM from rabbits, mice, monkeys and humans contains activated satellite cells, as identified by HGF and MyoD expression (McLoon and Wirtschafter, 2002a,b, 2003; McLoon *et al*, 2004). Normal LM from rabbits and humans also contain MyoD-positive satellite cells (Goding *et al*, 2005).

Many laboratories have examined the numbers of satellite cells associated with individual myofibres in limb SkM. Generally most limb SkMs fibres have between 0 and 10 satellite cells per myofibre

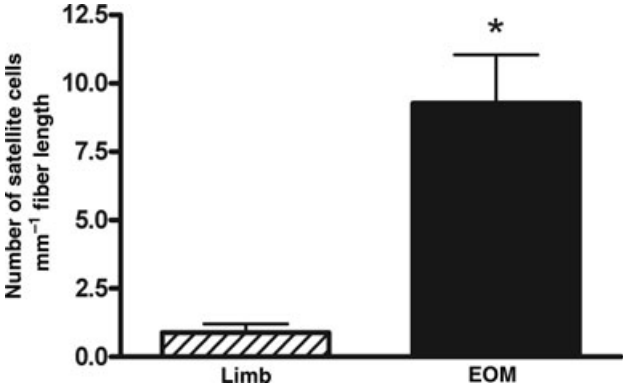

Figure 2 Quantification of the number of satellite cells identified by immunostaining for Pax7 calculated per mm fibre length on single isolated myofibres. Asterisk (*) indicates significant difference from limb muscle

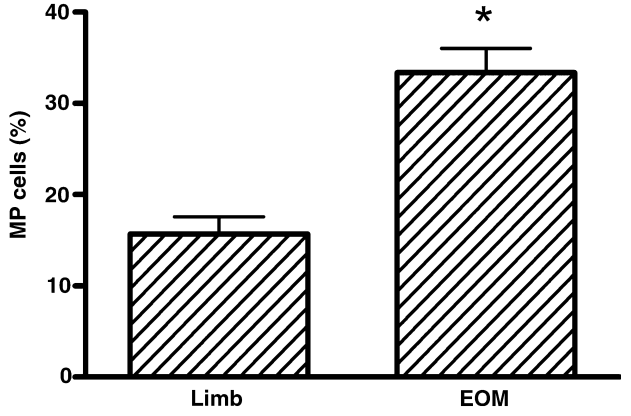

Figure 3 Using the Hoechst dye exclusion assay, the percentage of live cells that fall in the main population gate (MP) is approximately twofold higher in cell derived from rabbit extraocular muscle than those from rabbit limb skeletal muscle ($N = 10$). Asterisk (*) indicates significant difference from limb muscle

(Beauchamp *et al*, 2000; Wozniak *et al*, 2003; Kadi *et al*, 2004b; Sajko *et al*, 2004) but there is a great degree of variation. Using isolated fibres *in vitro*, extensor digitorum longus had seven satellite cells per myofibre, while soleus was shown to have 26 (Zammit *et al*, 2002). Preliminary immunohistochemical and cell sorting studies indicate that there are significantly more satellite cells within the EOMs. Using Pax7 immunostaining on single isolated myofibres, there were 10 Pax7-positive satellite cells per mm fibre length. If the average EOM myofibre is 7 mm long, this translates into 70 satellite cells per myofibre (Figure 2). This observation of a greater number of satellite cells associated with CSkM compared with limb muscle was also seen with the masseter muscle. There are a higher proportion of satellite cells in young adult masseter compared with young adult biceps, whereas the proportion was similar in both muscles in aged adults (Renault *et al*, 2002).

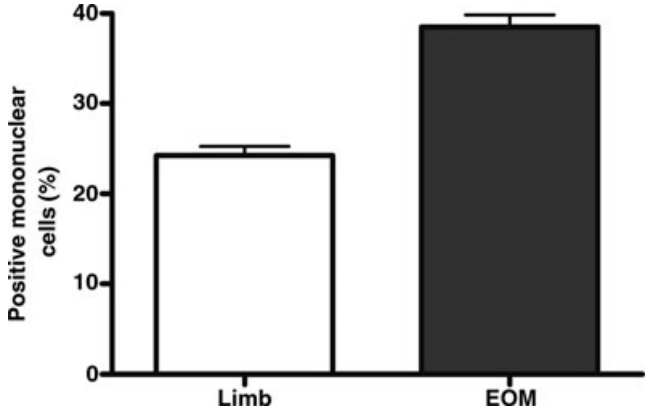

Figure 4 Freshly isolated mononuclear cells from extraocular muscle and limb muscles were fixed and permeabilized, then stained with antibodies for CD34 and Pax7. Bars represent the percentage of mononuclear cells stained positive for both markers

Many laboratories use the Hoeschst dye exclusion assay to divide the mononuclear cells from muscle into two populations: the main population, which retains the dye and is considered to enrich for satellite cells, and the side population, which actively eliminate the dye and is considered to enrich for more multipotent precursor cells. Using flow cytometric analysis and the Hoechst dye exclusion assay, the EOM contain twice as many cells in the main population gate when compared with the number isolated from limb muscle (Figure 3; McLoon *et al*, 2005). In addition, our preliminary examination of specific myogenic precursor cell markers on mouse myogenic precursor cells analysed by flow cytometry show that approximately 40% of the live cells are positive for the satellite cell markers Pax7 and CD34 compared with only 23% in those from limb muscle (Figure 4). Published reports and our preliminary data support the hypothesis that the EOM and other craniofacial muscles have important intrinsic differences in their populations of myogenic precursor cells compared with limb muscle. We are particularly interested in comparing muscles within the CSkM and that work is ongoing.

Table 1 Summarizes investigations into therapeutic potential of muscle-derived cells for various target tissues

Skeletal muscle	Isolation and characterization of myogenic cells is a central area of ongoing research; 'homing' mechanisms are being examined. Cellular characteristics may also vary over time. Rejection, effects on strength and durability are key efficacy issues	Alessandri *et al* (2004); Deasy *et al* (2004); Jankowski *et al* (2002); Lee Pullen and Grounds (2005); Partridge (2003); Qu-Petersen *et al* (2002); Torrente *et al* (2003)
Heart muscle	Phase I/II clinical trials of transplanting myoblasts into patients with previous myocardial infarction are gen erating promising data with evidence of contractility, improved left ventricular function, and vascularity – methodological issues still remain, however	Gavira *et al* (2006); Kessler and Byrne (1999); Marelli *et al* (1992); Menasche *et al* (2001); Pandur (2005); Smits *et al* (2003); Taylor *et al* (1998); Yoon *et al* (2005)
Smooth muscle	Most studies using transfer of skeletal muscle-derived cells have been targeted towards the urinary tract notably improving detrusor muscle function, with some evidence of transdifferentiation towards a smooth muscle phenotype	Yokoyama *et al* (2001); Huard *et al* (2002)
Bone	Increasing knowledge in development in relation to specific osteogenic signalling factors, such as expression of bone morphogenic proteins has enabled improved osteo-induction. However, long-term translation of *in vitro* data are awaited	Asakura *et al* (2001); Cornelison and Wold (1997); Kaplan *et al* (2004); Sampath *et al* (1984); Shen *et al* (2004); Urist *et al* (1970)
Fat	There is now *in vitro* and *in vivo* evidence of muscle-derived stem cells undergoing adipogenic differentiation under various conditions of disease/ injury and denervation, i.e. 'muscle does indeed turn to fat'; therapeutic applications yet to be fully explored	Dulor *et al* (1998); Rudnicki *et al* (1993); Yamanouchi *et al* (2006); Young *et al* (2001)
Nervous tissue	Demonstration that neurogenic differentiation is clearly possible, but uncertainty remains in terms of potential cellular functionality/specificity. Ongoing research into tissue engineering of neuromuscular junctions may 'bridge the gap' between neurological and myogenic cell interaction	Alessandri *et al* (2004); Qu-Petersen *et al* (2002); Romero-Ramos *et al* (2002); Vourc'h *et al* (2004); Young *et al* (2004)

Can the CSkM satellite (stem) cell population commit to other, non-myogenic, phenotypes and does their embryological origin confer increased potentiality

The data presented thus far points to a satellite (stem) cell population in CskM that is more active than in non-craniofacial muscle groups and expresses a whole number of features indicative of a highly adaptive cell type. An intriguing possibility is that this activity could be harnessed to regenerate or repair tissues other than SkM. There is only one study that has addressed the specific issue of CSkM derived multipotent precursor cells, and that is from jaw muscles, but there are many looking at such cells from non-craniofacial muscle. Table 1 summarizes investigations into therapeutic potential of muscle-derived cells for various target tissues.

Our own work on cells derived from human masseter muscle has indicated that not only does the non-myogenic cellular component have the ability, when given the appropriate cues, to differentiate along the adipogenic and osteogenic lineages, but that a small proportion of cells within a population apparently committed to the myogenic lineage (sorted by expression of myogenic surface markers) are also able to differentiate outside of the myogenic lineage (Sinanan *et al*, 2004). These cells appear to co-express both stem-like markers (CD34) and myogenic markers (CD56); it remains unclear as to whether this is a feature of all muscle-derived cells or only those from CSkM.

The suggestion is therefore developing that cells from CSkM (including those derived from satellite cells) are able to commit to non-myogenic lineages and that the craniofacial origin may confer additional advantages; the latter is something that our group are currently in the process of determining.

Conclusion

The unique ability at least some of craniofacial muscles to retain a population of activated satellite cells that provide for continuous myofibre remodelling throughout life suggests that there may be intrinsic differences in proliferative and myogenic properties of the satellite cells in these muscles. If the myogenic precursor cells within the CSkM retain these proliferative properties even in ageing muscle, this suggests that they may be more robust and long-lived than myogenic precursor cells from limb muscles after transplantation into a host muscle. If these hypotheses are true, we may be able to exploit this by using the myogenic precursor cells from CSkM as a source of donor cells in myoblast therapy for Duchenne and related muscular dystrophies or as a novel source of cells for repair of other tissues such as bone.

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