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Review

The satellite cell as a companion in skeletal muscle plasticity: currency, conveyance, clue, connector and colander

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Summary

Satellite cells are companions to voluntary muscle fibres, and are named for their intimate positional or 'satellite' relationship, as if revolving around fibres, like a satellite moon around the earth. Studies on the nature of at least some satellite cells, including their capabilities for self-renewal and for giving rise to multiple lineages in a stem cell-like function, are exploring the molecular basis of phenotypes described by markers of specialized function and gene expression in normal development, neuromuscular disease and aging. In adult skeletal muscle, the self-renewing capacity of satellite cells contributes to muscle growth, adaptation and regeneration. Muscle remodeling, such as demonstrated by changes in myofibre cross-sectional area and length, nerve and tendon junctions, and fibre-type distribution, occur in the absence of injury and provide broad functional and structural diversity among skeletal muscles. Those contributions to plasticity involve the satellite cell in at least five distinct roles, here described using metaphors for behaviour or the investigator's perspective. Satellite cells are the 'currency' of muscle; have a 'conveyance' role in adaptation by domains of cytoplasm along a myofibre; serve researchers, through a marker role, as 'clues' to various activities of muscle; are 'connectors' that physically, and through signalling and cell-fibre communications, bridge myofibres to the intra- and extra-muscular environment; and are equipped as metabolic and genetic filters or 'colanders' that can rectify or modulate particular signals. While all these roles are still under exploration, each contributes to the plasticity of skeletal muscle and thence to the overall biology and function of an organism. The use of metaphor for describing these roles helps to clarify and scrutinize the definitions that form the basis of our understanding of satellite cell biology: the metaphors provide the construct for various approaches to detect or test the nature of satellite cell functions in skeletal muscle plasticity.

Key words: muscle regeneration, activation, myogenesis, fibre, nitric oxide, gene expression, heterogeneity, transplantation.

What is a 'satellite cell' in skeletal muscle?

The satellite cell in skeletal muscle is one of the many cell types in the body that is named for its location. Satellite cells are located in an 'intimate' position next to the comparably huge extrafusal fibres that comprise the belly of a voluntary muscle. Mauro first proposed the nomenclature (Mauro, 1961). Satellite cells have a unique relationship with individual muscle fibres, and serve a multifaceted role in adaptation and plasticity of skeletal muscle. While the origin of satellite cells was in question for many years, they are designated in development by Pax7 expression (Seale et al., 2000; Seale et al., 2004b). There is a narrow cleft of a very consistent dimension, between a satellite cell and a myofibre (Fig. 1), identified by electron microscopy.

Early satellite cell literature

At a conference on regeneration of striated muscle and myogenesis in 1969, Milhorat reported (Milhorat, 1970):

'*The potential of striated muscle to regenerate generally is not appreciated by biologists and clinicians, although, under appropriate conditions, this regenerative capacity may be considerable. This phenomenon obviously is of much scientific and clinical interest. … and has great significance to the hypothesis and practice of medicine... Biologists find of particular interest, the origin and myogenic nature of the mononucleated cells found between the basement membrane and the plasmalemma, and the relation of these cells to myoblasts. Many investigators postulate that these mononucleated cells, so-called satellite cells, represent reserve myoblasts that could reproduce by mitotic division, the newly*

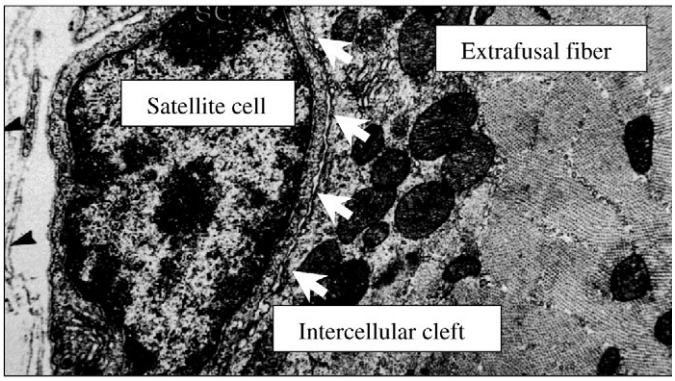

Fig. 1. An electron micrograph of a satellite cell closely applied to the sarcolemma of an extrafusal fibre. The satellite cell is covered by a thin layer of basement membrane (black arrowheads; also called external lamina), which does not appear between the fibre and satellite cell (original magnification ×30 000).

formed cells fusing to form myoblasts and finally multinucleated muscle fibres.'

That conference was a landmark in studies of the satellite cell and muscle regeneration, and was attended by many of the notable and pioneering contributors to the field of muscle development and muscle regeneration. Muir summarized the debate on a working definition of the satellite cell, as follows (Muir, 1970):

'*The satellite cell of striated muscle can be defined as a mononucleated cell, whose cytoplasm does not contain myofilaments, and which is enclosed by or lies within the basement membrane component of the sarcolemma of the striated muscle fibre. This definition does not exclude cells which are partially or completely separated from the muscle fibre plasma membrane by extensions of the basement membrane, providing that the basement membrane forms a complete investment of their outer surfaces.*'

Although there were presentations detailing the observed uptake of ^{3}H-thymidine into nuclei of satellite cells (Hay, 1970), the role of satellite cells as precursors was not fully established in 1969. In fact there was still very strong debate that a muscle fibre could fragment into blastema cells that led to new formation of muscle. Even at this time, there was more than one paper on the appearance of osteogenic and chondrogenic tissues from minces of muscle replaced under the skin, and a report of muscle fibre nuclei contributed by a labelled connective tissue grafted into a salamander limb during regeneration (Steen, 1970).

It wasn't until two seminal reports from the laboratory of Dr Charles Leblond at McGill University (Moss and Leblond, 1970; Moss and Leblond, 1971) that skeletal muscle satellite cells were convincingly identified as the source of precursor cells that proliferate and fuse to form new skeletal muscle fibres. Time-course studies of labelled nuclei in growing muscle showed that satellite cells were the only muscle cells that had incorporated ^{3}H-thymidine. The report followed work on colchicine-treated rats (MacConnachie et al., 1964) that showed mitotic figures only in the peripheral 'satellite' position on muscle fibres. The idea that muscle fibre nuclei give rise to the increasing number of myonuclei during the growth was convincingly ruled out (Enesco and Puddy, 1964). The notion that satellite cells contribute these domains to a growing or regenerating fibre, one at a time, is daunting in light of the expenditure of proliferative energy and fusion events. However, it speaks strongly to one of the major roles of satellite cells as a currency of muscle (see below).

Satellite cells were also observed on intrafusal fibres (Katz, 1961). Two types of satellite cells were identified on these so-called muscle spindle fibres and were distinguished from those on extrafusal fibres (Maynard and Cooper, 1973), although at least one would now be called a myoblast.

Although typically quiescent in normal adult muscle, satellite cells are generally considered to be committed to the myogenic lineage. They become activated and recruited to the cell cycle when there is a requirement to increase myonuclear number in growth, adaptation and regeneration (e.g. Darr and Schultz, 1987; Schultz and McCormick, 1994).

This historical examination of the satellite cell literature therefore identifies a few lessons: (1) nomenclature can change the perspective of view, and shape the literature; (2) careful, painstaking investigations that use more than one tool (e.g. radioautography and histology or electron microscopy) to study one variable are powerful in dissecting the underlying basis of observations; and importantly to this review, (3) satellite cells are the only source of proliferative muscle precursors and thence new myonuclei, in normal growing muscle.

Satellite cell activation

Even minor perturbations to a muscle can alter the quiescent appearance of thin and attenuated satellite cells adjacent to fibres, as evidenced in a variety of muscle diseases. The alterations take the form of cell swelling, expanded organelles and lower chromatin density. These changes demonstrate structurally that satellite cells have become activated, and have departed from quiescence and entered the G_1 phase of the cell cycle.

Our work on satellite cell activation developed from an interest in the causality of the myogenic regeneration response that was described to ensue from injury (Fig. 2), exercise, loading of muscle or skeletal segments of the body, and from denervation. We demonstrated a role for nitric oxide in mediating muscle regeneration in mice with deficient NO production secondary to dystrophin mutation, primary mutation in NOS-1 or NOS inhibition, from observing delayed activation after injury (Anderson, 2000) (Fig. 3). The notion of nitric oxide as a mediator of satellite cell activation and regeneration led to the notion that nitric oxide helps to regulate activation and quiescence (Anderson and Wozniak, 2004; Wozniak et al., 2005; Wozniak and Anderson, 2005). Experiments on mdx mice identified that nitric oxide promotes muscle regeneration and partly alleviates mdx mouse

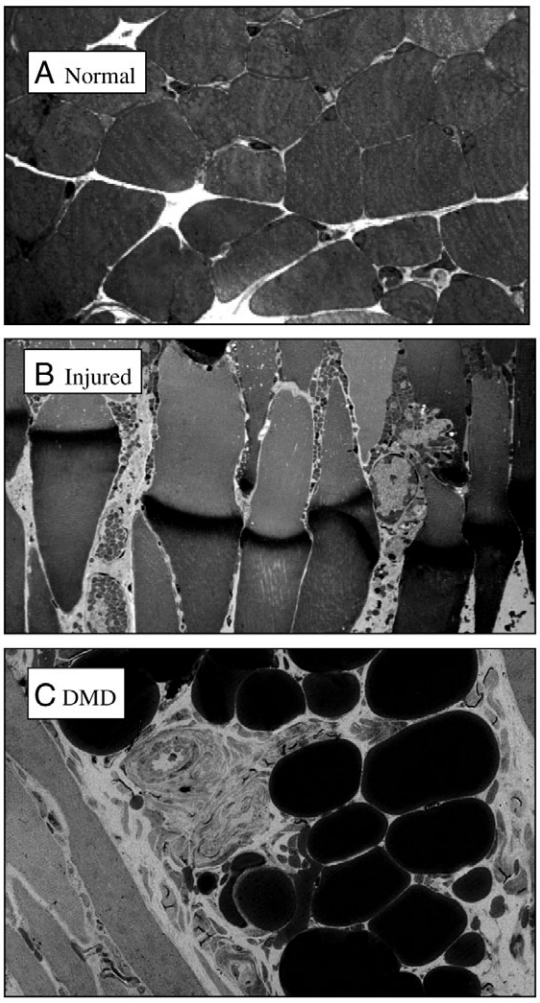

Fig. 2. (A) Normal skeletal muscle in transverse section showing muscle fibres separated by endomysial connective tissue and small profiles of vascular supply. Part of a muscle spindle is visible toward the bottom left of the micrograph. Satellite cells are impossible to identify at this magnification. (Original micrograph ×140; Toluidine Blue staining.) (B) Normal muscle in longitudinal section, some 10 min following traumatic injury. Fibres are broken and show hypercontracted myofibrils. There is extravasation of red blood cells from a damaged vessel into the interstitial space. (Original micrograph ×140; Toluidine Blue staining.) (C) Micrograph of a section of skeletal muscle from a muscle of a patient with Duchenne muscular dystrophy. While there are some fibres of muscle present (to the left of the field), much of the field is filled with dense collections of collagen bundles and adipocytes (central and right of the field). (Original micrograph ×140; Toluidine Blue staining.) Much of the pathology literature on DMD refers to muscle being replaced over time by adipose and connective tissues as muscle fibres are damaged and the disease progresses. However, there is a distinct possibility that the adipocytes and fibroblasts may have differentiated from stem cells in the satellite cell position on fibres, since this alternate differentiation can be observed in tissue culture and in aging muscle (Jozsi et al., 2001; Shefer et al., 2004; Taylor-Jones et al., 2002). Other descriptions of 'transdifferentiation' are reported between vascular smooth muscle and skeletal muscle and may relate to the apparent pool of stem cells in the mesangioblast compartment in development (Cossu and Bianco, 2003; Galli et al., 2005; Graves and Yablonka-Reuveni, 2000; Sampaolesi et al., 2003).

muscular dystrophy (Anderson and Vargas, 2003; Tidball and Wehling-Henricks, 2004b; Wehling et al., 2001). Very recently, further details of the very tightly regulated nitric oxide signalling in myoblast fusion and myotube growth, studied in developing myoblasts and in satellite cell cultures, were elegantly demonstrated to occur *via* cyclic guanosine monophosphate (cGMP) and induction of follistatin expression (Pisconti et al., 2006). Other signals among different tissues and cells form the contextual environment of the satellite cell and those cells are also anticipated to receive signals from satellite cells in various conditions of quiescence and activity during plastic changes in muscle.

Satellite cell gene expression

Early characterization of myogenesis and muscle regulatory gene expression by satellite cells after activation (Cornelison and Wold, 1997) identified that c-met receptor was expressed in both quiescent and activated satellite cells. C-met is also expressed by other cells, including hepatocytes, lung and gut epithelium and pericytes, and is noted as an important regulator of mobility and migration, particularly in metastatic processes (Abounader et al., 2001; Liou et al., 2002; Maulik et al., 2002; Parr and Jiang, 2001). Satellite cells isolated from skeletal muscle are characterized as having the gene expression profile: Pax7+, CD34+, CD45–, Sca1– (Montarras et al., 2005).

Other markers of stem-like functions (self renewal, a latent or very low cycling rate, multiple potential for lineage differentiation), such as those of the hematopoietic lineage, have also been explored as markers of muscle stem cells, with considerable debate in the literature related to techniques of cell isolation from muscle, and the precise controls established in protocols for fluorescence-activated cell sorting (FACS) techniques. Once they migrate outside the external lamina, activated satellite cells are variously referred to as muscle precursors or myoblasts to denote their myogenic lineage. Experiments using separation of stem-like cells from skeletal muscle by FACS analysis have provided a large body literature on the genetic phenotype of the more 'stem-like' cells (e.g. Asakura et al., 2001; Asakura et al., 2002; Cahill et al., 2004; Cao et al., 2003; Collins et al., 2005; Deasy et al., 2001; Holterman and Rudnicki, 2005; Jankowski et al., 2001; Jankowski et al., 2002; O'Brien et al., 2002; Seale et al., 2004b; Seale and Rudnicki, 2000). By separation of a well-defined population of satellite cells from muscle tissue, through sorting on the level of expression of one gene for example, or the nature of calcium handling and dye exclusion through carefully controlled experiments (Montanaro et al., 2004), the population can be 'interrogated' for the expression of a second gene or characteristic. This approach has given significant information on proliferative capacity relative to the features of precursor morphology, adhesion in tissue culture plates, fusion capacity, and the nature of lineages that may arise from cells with a particular expression profile. As well, magnetic resonance imaging techniques have been utilized to track stem cells *in vivo* by pre-labelling with contrast agents that allow detection of as few as eight cells, or the myotubes produced

following differentiation of the daughter cells arising from the injected or grafted stem cells in a muscle (Cahill et al., 2004; Hoehn et al., 2002; Pastor, 2005).

Modelling satellite cells in myogenesis using single muscle fibres

Current investigations on the stem-like nature of satellite cells are developing important data to support hypotheses of a capacity for self renewal. Satellite cells are defined by their position on fibres inside the basement membrane, a layer that remains covering satellite cells and the fibres after gentle digestion of muscles in collagenase. That layer surrounds fibres that are plated for culture in the model of single isolated fibres (Fig. 4). That model was developed in tandem with the use of single mammalian muscle fibres for contractility experiments, through the use of digestion and/or fine dissection techniques (used earlier in amphibian muscle experiments on contractility), and is reported with increasing frequency as a valuable adjunct to investigations of satellite cell biology. Stem cells, however, are defined more according to their functional capacity to self-renew. That capacity is apparently seriously reduced, at least in skeletal muscle tissue and in bone marrow, by the negative but not well understood effects of the protease digestion techniques (e.g. collagenase, pronase) used to separate satellite cells from myofibres or hematopoietic stem cells from bone marrow (Collins et al., 2005). Indeed, the difficulty of studying stem cells *in vivo* is highlighted in many tissues, and often in experiments that show a contribution of non-muscle tissues to muscle regeneration or to provision of muscle-resident cell populations (Cossu, 2004; Cossu and Bianco, 2003; Dezawa et al., 2005; Ferrari et al., 1998; Galli et al., 2005; Gros et al., 2005; Pagel et al., 2000).

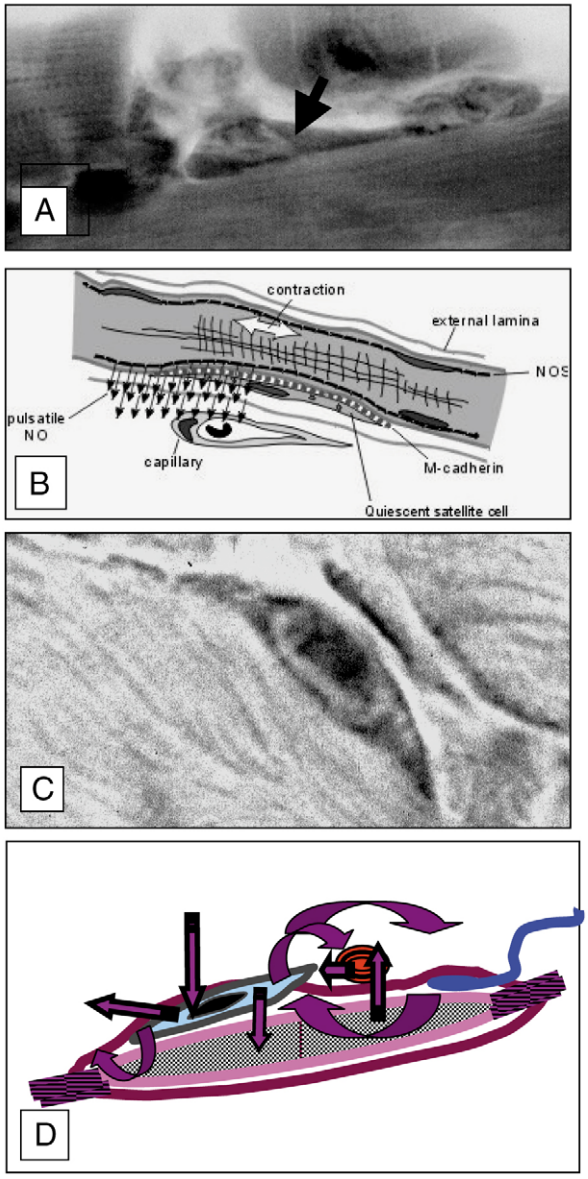

Fig. 3. (A) An activated satellite cell on a muscle fibre 10 min following injury (arrow). (Original micrograph taken at ×350; H&E staining.) (B) Schematic depicting the relative location of NOS-1-derived nitric oxide release from a muscle fibre and diffusing through satellite cell toward the interstitial space (after Anderson, 2000). (C) Micrograph of NOS-1 expression in an activated satellite cell in skeletal muscle. (Original micrograph ×350; *in situ* hybridization) (after Anderson and Vargas, 2003). (D) A schematic describing potential communication and feedback signaling among various compartments, cells and tissues in skeletal muscle, suggesting that satellite cells are active as filters for signaling during structural and functional plasticity.

Heterogeneity of muscle satellite cell populations

Many experiments have suggested there is more than one type of muscle precursor [reviewed recently (Wozniak et al., 2005)]. For example, it is suggested that ongoing regeneration in muscular dystrophy may exhaust one of two types of satellite cells (Heslop et al., 2000) (A. C. Wozniak and J.E.A., unpublished observations).

An elegant report on the stem-cell niche of satellite cells on fibres (Collins et al., 2005) has convincingly demonstrated that satellite cells themselves, defined anatomically, indeed demonstrate self-renewal, and have a very high capacity to proliferate and regenerate new muscle. Normal muscle fibres with resident satellite cells, rather than myoblast injections, were injected into dystrophin-deficient muscle, and the satellite cell progeny reconstituted significant numbers of dystrophin-positive fibres in dystrophic muscle. That success included major contributions to the myonuclei and, importantly, to renewal of the satellite cell compartment in those regenerated fibres. This report provides critical evidence that satellite cells do return to quiescence after contributing to muscle regeneration. Earlier work demonstrated that satellite cells retain some features of the source muscle, for example after transplantation, and yet that there is marked heterogeneity among the cells that grow from even one single fibre in a muscle (Parry, 2001). There may be no need to invoke ‘stem cells’ as a distinct subset of the cells that are positioned in the satellite position on fibres for muscle regeneration (Collins et al., 2005). The precise mechanism that accounts for significant improvement in transplantation by injection of satellite cells on intact fibres, rather than injection of purified cell suspensions,

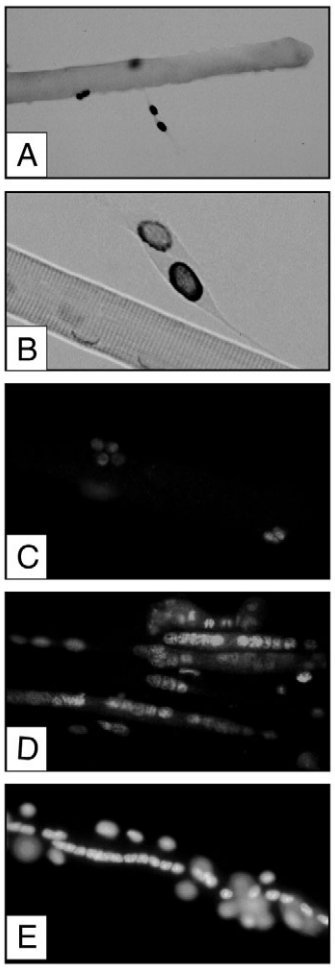

Fig. 4. (A) A single normal muscle fibre isolated from the flexor digitorum brevis muscle of a normal mouse. The fibre was maintained in culture for 48 h in the presence of bromodeoxyuridine (BrdU) to label DNA synthesis. Two satellite cells are adherent to the fibre; two additional cells (not identifiable with this staining technique) lie on the surface of the culture dish and have also incorporated BrdU during culture. Note that the post-mitotic nuclei within the muscle fibre have not incorporated BrdU. (Original micrograph ×60.) (B) A single normal muscle fibre with BrdU-positive satellite cells beginning to migrate away from the fibre. Again, myonuclei inside the muscle fibre are not BrdU-positive. (Original magnification ×140.) A and B after (Anderson and Pilipowicz, 2002). (C) A single normal muscle fibre prepared by immunostaining to demonstrate myogenin expression in activated satellite cells that are undergoing myogenesis on the fibre. The satellite cells have likely divided since the fibres were originally plated for culture, as they are present in pairs and quartets on the fibre surface. Note that the myofibre nuclei do not express myogenin, a muscle-specific regulatory gene expressed during the differentiation phase of myogenesis. (Original magnification ×140.) (D) A selected field of myotubes in tissue culture, showing myogenin protein expression by immunostaining and fluorescence microscopy. Cultures are plated satellite cells isolated from skeletal muscle, and may contain 'contaminating' cells of the fibroblast, adipocyte and endothelial lineages that are only partly distinguishable from myogenic cells in unstained cultures using structural and behavioural phenotypes. Myotubes form in culture as a result of cell fusion events, meaning that many myogenic cells were contained in a culture. Only those mononuclear cells expressing myogenin would be identified as myogenic. (Original magnification ×140.) (E) A single dystrophic muscle fibre isolated from the flexor digitorum brevis muscle of an mdx dystrophic mouse, showing nuclei stained with DAPI (Z. Yablonka-Reuveni and J. E. Anderson, unpublished data). Nuclei are present within the fibre in one of three phenotypes. In the longitudinal regions or segments that have not undergone degeneration and regeneration, the nuclei are apparently 'jumbled' and mainly appear out of the plane of focus. In other longitudinal segments of the fibre, the myonuclei are displayed as rows of centrally placed nuclei; these segments have undergone a cycle of degeneration and regeneration, and these central myonuclei originated from the fusion of satellite cell progeny into the muscle fibre remnant. The same regenerated segments are 'decorated' with satellite cells, the nuclei of which appear at the periphery of the fibre. These cells lie outside the sarcolemma and within the external lamina that is present on these isolated fibres (Wozniak et al., 2003) and have contributed, through proliferative events, the myonuclei that lie within the adjacent regenerated segments. Note that this technique does not identify the possible heterogeneity between satellite cells regarding the number of cell cycles that have passed, and that the 'parent' satellite cell may not lie in the same segment as the central myonucleus that was generated by the previous cell cycle. (Original magnification ×140.)

is not known. The nature of events within those satellite cells, such as 3-way signaling among satellite cells, fibres and the host environs, which promote the improved outcome from this approach, remains to be determined.

Plasticity

Plasticity is adaptability to change or flexibility, in response to functional demands, with consequent modifications to structural and/or functional phenotypes. In biology, phenotypic plasticity is an ability of a genotype to express different phenotypes, adaptive or environmentally constrained by experience.

It is worth considering the role of terminology and dogma as the glasses that shape our vision and understanding of the functional significance of plasticity. Quesenberry tackles this construct directly by questioning the hierarchical patterning of lineage development that extends through the literature (reviewed by Quesenberry et al., 2005). The reports outlines that stem cells do cycle, either slowly and continuously or infrequently and sporadically, and are therefore not 'quiescent', although depending on experimental design may appear mitotically or metabolically very inactive. Clonal studies always demonstrate heterogeneity, despite sorting on the basis of standard stem-cell markers, and the ability of a cell to cross lineage boundaries (e.g. from bone marrow to skeletal muscle) depends exquisitely on the precise phase of the cell cycle when a particular stem cell is exposed to some signal. A 'continuum model of stem cell regulation' is described, in which mid-S-phase provides the maximum responsiveness to differentiation-inducing signals. The potential of stem cells to respond to a signal that induces differentiation will change through the cell cycle, and is evidenced by what is described as differentiation 'hot spots'. The new interpretation of satellite

cell function that is provided by the notion of a 'plasticity continuum', meaning the full range of responses between cycling and differentiation, provides an intriguing insight into the 'spectrum' of roles that may be developed by a skeletal muscle stem cell, the satellite cell, in muscle plasticity. Reviews elsewhere in this issue, on functional, structural and molecular plasticity of mammalian muscle, environmental influences on fish muscle plasticity, and coordination of metabolic plasticity in skeletal muscle, will provide additional insights, not reiterated here in detail.

Skeletal muscle plasticity

Regarding adaptations to change function, gene expression and structural phenotype in relation to demand or environmental pressure, satellite cells are the 'agent' of rapid, prolonged and persistent change during muscle development, growth, responses to disease or injury, and regeneration. This plasticity of skeletal muscle has been described in relation to (1) stem cells (historically described in the hematopoietic cell lineage, and in the muscle literature exploring the distinctive nature of lineages for fibres of a fast-glycolytic, slow-oxidative, or oxidative-glycolytic phenotype) (Duxson et al., 1989; Gussoni et al., 1999; Gussoni et al., 2002; Harris et al., 1989; Johnston et al., 2000; Johnston and Temple, 2002; Mouly et al., 1993; O'Brien et al., 2002; Parry, 2001; Rosenblatt et al., 1995; Rosenblatt et al., 1996), (2) the trans-differentiation across cell lineages and even germ-layer origins (e.g. Bottai et al., 2003; Cossu and Bianco, 2003; Galli et al., 2005; Vescovi et al., 2002), (3) cell fusion (which may appear similar to a stem cell differentiating into a new lineage when it is transplanted or placed into the niche of a new tissue) (Goodell et al., 2001; Jackson et al., 2002; McKinney-Freeman et al., 2002), (4) adaptation (as in the response to exercise, disuse or aging) (e.g. Allen et al., 2001; Caccia et al., 1979; Harrison et al., 2002; Renault et al., 2002; Thornell et al., 2003), (5) regeneration (as from injury or degenerative neuromuscular and neurological diseases) (e.g. Galli et al.. 2005; Harris, 2003; Martino, 2004; Sohn and Gussoni, 2004; Sugaya, 2003a; Sugaya, 2003b) and (6) development (which distinguishes between genetic and other signaling events that lead to the fiber architecture of a particular muscle, body segment or the vascular supply in a muscle anlage) (e.g. Brand-Saberi, 2005; Brand-Saberi and Christ, 1999; Denetclaw, Jr et al., 2001; Denetclaw and Ordahl, 2000; Duxson et al., 1986; Ordahl, 1999; Williams and Ordahl, 2000).

Muscle tissue is known to adapt to various uses across many species. It is organized in fibre arcades with each fibre attached to a relatively more rigid structure for transfer of force. Consider a columnar arcade (Fig. 5): if the floor or ceiling attachments of the columns are required to be moveable, and also to be changeable or adaptable during that base motion, then some specialization of the junctions of a column to each attachment will be required. In skeletal muscle tissue, this attachment is typically a muscle–tendon junction or Sharpey fibre, and there are satellite cells nearby, often activated in that location. Along the length of the column (the fibre), there is a sarcomeric regularity in myofibrils. However, continuous use of muscle requires protein turnover in the cytoplasmic regions (domains) regulated by each nucleus, and also replacement to maintain functional capacity. This turnover involves plasticity, enabled by nearby satellite cells. Tissue maintenance is normal, and adaptations of a fibre to increased or decreased demand come well within the scope of normal, periodic muscle plasticity. While muscle regeneration following damage to a segment of the fibre column is generally only sporadically required in normal muscle, it poses a major demand for muscle plasticity provided by the satellite cell, during severe injury and in the course of many neuromuscular diseases.

Adaptive remodeling of skeletal muscle is demonstrated by changes in myofibre cross-sectional area, fibre length, the number of sarcomeres in series and in parallel, the number and functional capacity of mitochondria, the configuration of cellular junctions of muscle fibres with tendons and nerves, fibre-types, and motor units. And there are signals that travel back to motor neurons and thence to the central nervous system to coordinate these changes in an integration of function and motor patterning. However, contributions to plasticity also involve the satellite cell as a companion to the fibre, in at least five distinct roles, including as currency, conveyance, clue, connector and colander.

(1) Satellite cells as currency

Satellite cells are truly the 'currency' of muscle tissue. They are the operational 'cash-units' that 'purchase' muscle formation, which supports adaptation for functions including contractility and thermogenesis. Through proliferation, generations of satellite cell progeny are muscle building blocks in development and regeneration. Expression of muscle-specific regulatory genes directs differentiation as the nuclei of satellite cell progeny contribute incremental increases in the transcriptional capacity to a myofibre by fusing to the fibre sarcolemma. Satellite cells are therefore fundamental to the requirements for growth and to meet changing demands, although growth doesn't necessarily invoke a change in the net functions of myofibre nuclei. In the course of fusion with a fibre, the satellite cell progeny bring the inherent developmental program that guides synthesis of proteins, from embryonic to neonatal to adult (e.g. for myosin heavy chains). This is recognized in observations of segmental expression of developmental myosin (e.g. Pernitsky et al., 1996).

Muscle regeneration also requires the expenditure of the currency comprising satellite cell progeny (Fig. 4). Fibre damage, either focal in trauma (Schultz et al., 1985) or induced by pathology that is intrinsic to fibres (Cooper, 1989; Hoffman et al., 1987; Kunkel and Hoffman, 1989; Lefaucheur et al., 1995) or extrinsic, e.g. ischemia (Authier et al., 1997; Hansen-Smith and Carlson, 1979; Makitie and Teravainen, 1977a; Makitie and Teravainen, 1977b), induces myogenic cells to become activated, proliferate and fuse to form new fibres that elongate between mature fibres. Eventually new fibres attach to tendons to deliver a functional gain.

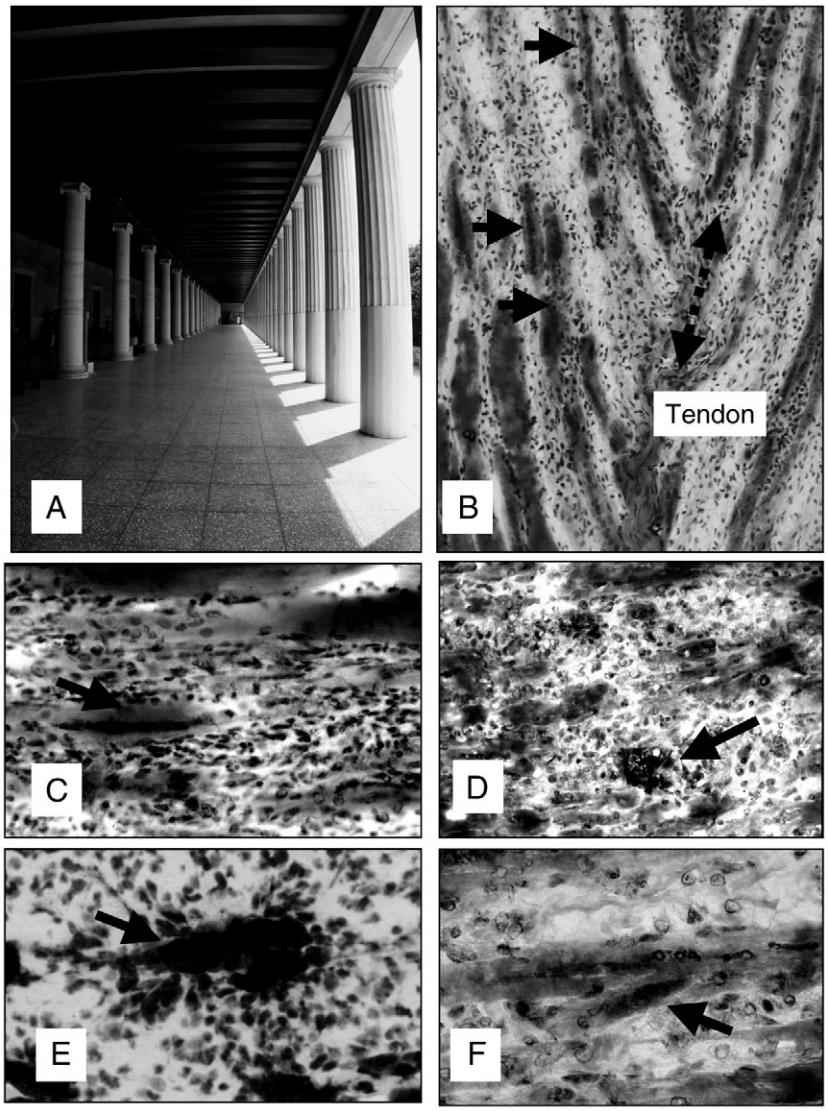

Fig. 5. (A) A columnar arcade in which plasticity of function or form is not integrated into the design. (original photograph, Agora, Athens, Greece). (B) This micrograph of skeletal muscle regenerating after traumatic injury contrasts with the arcade of Greek columns in A. A tendon courses through the figure vertically (broken line) and is met by myotubes (arrows) forming in the belly of the damaged muscle. In the damaged region, many myogenic cells (progeny of satellite or stem cells) are present, admixed with numerous mononuclear cells that are only partly identifiable as inflammatory, phagocytic, fibroblastic or angiogenic. The myotubes contain numerous central myonuclei, indicating they have been formed in a regenerative process in the 6 days since injury. The tendon and myotubes, vascular and connective tissues are all involved in the regenerative events that support the plasticity of this skeletal muscle. (Original micrograph at ×60.) (C) Myotubes forming by regenerative events at 4 days after injury, showing accretion of nuclei and expansion of the myofibre diameter (arrow). (Original micrograph at ×140.) (D) Myotubes and mononuclear cells in the bed of a regenerating muscle following injury. In this field, there is a small central area of ossification (arrow), in a region where no osteogenic progenitors would have been identified prior to injury. The formation of bone in a muscle also demonstrates plasticity of satellite cells in taking direction to be precursors for alternate mesenchymal tissues (Deasy et al., 2004); Lee et al., 2000; Shen et al., 2004). (Original micrograph at ×140.) (E) A myotube (arrow) forming through addition of myogenic cells, identified (by *in situ* hybridization) by their expression of myogenin transcripts, a muscle-specific regulatory gene. The myogenic cells are progeny of the satellite or stem cells that were activated by muscle injury. After proliferation, the cells migrate within the regenerating muscle bed, become aligned in the longitudinal axis of the muscle (which is still attached to the tendons and therefore subject to passive tension during locomotion) and fuse. Long filopodial processes can be observed extending toward the myotube from myogenin-expressing cells in the surrounding region of mononuclear cell infiltration. (Original micrograph at ×140.) (F) Micrograph showing a branched myotube (arrow), formed in a regenerating muscle during treatment with a NOS inhibitor. The fusion of myogenic precursors to myotubes or remnant stumps of damaged fibres is mediated in part by the level of nitric oxide in skeletal muscle, and with a low level of nitric oxide, the branched myotube phenotype predominates over the typical slender cylindrical myotubes that form in normal regenerating muscle (Anderson, 2000). (Original micrograph at ×140.)

Myogenic cells also enter the damaged segments of fibres while debris is cleared from within the basement membrane sheath, and then fuse to bridge the ends of remnant fibres. EM studies show the ‘resealing’ events at the surviving fibre membrane (Robertson et al., 1992). Notably, dysferlin mutations reduce the membrane recycling and induce a form of muscular dystrophy (Bansal et al., 2003; Bansal and Campbell, 2004). Experiments by Grounds and McGeachie and colleagues using muscle in longitudinal sections, confirmed and extended the nature of even earlier work (e.g. Schultz et al., 1978; Schultz et al., 1985; Carlson, 1995; Hansen-Smith and Carlson, 1979; Tank et al., 1977; Grounds and McGeachie, 1987; Grounds and McGeachie, 1989; McGeachie et al., 1993; McGeachie and Grounds, 1987), which showed that satellite cells must proliferate in this repair process. Repair capacity in denervated or tenotomized muscle is retained to a lesser extent, and in the longer term, is constrained by accumulation of interstitial collagen and reduced fusion (Borisov et al., 2005a; Borisov et al., 2005b; Dedkov et al., 2001; Dedkov et al., 2002; Lu et al., 1997; McGeachie, 1985; McGeachie, 1989).

Satellite cell proliferation is not seen as the limiting factor in muscle regeneration or growth, although that capacity may be exhausted in severe conditions such as muscular dystrophy (Collins et al., 2005; Blaveri et al., 1999; Bockhold et al., 1998; Goldring et al., 2002; Heslop et al., 2000; Morgan and

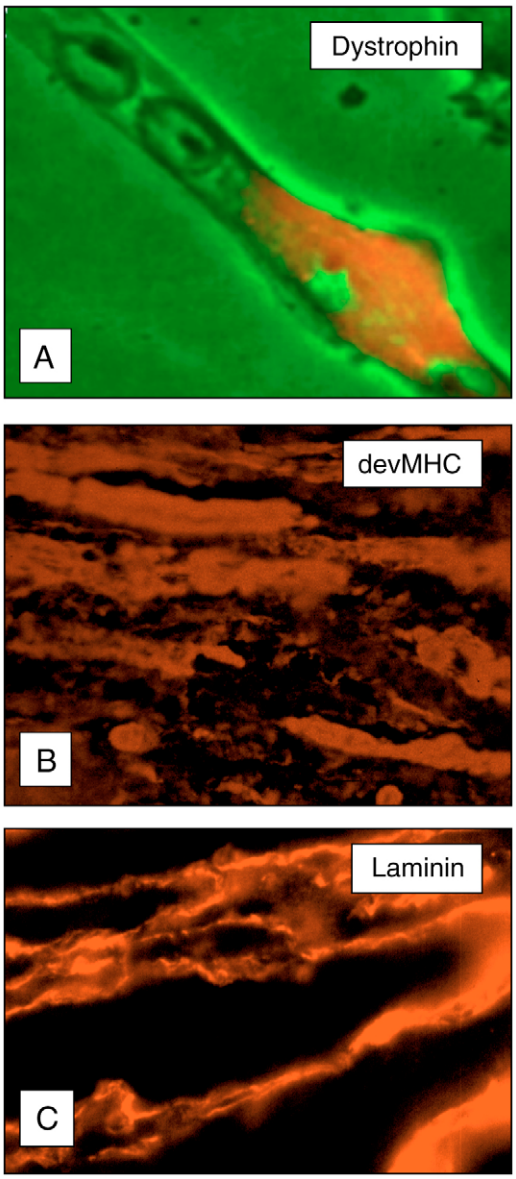

Fig. 6. (A) A region of a myotube around one nucleus (a cytoplasmic domain) that has contributed dystrophin expression to the myotube through fusion during myotube formation. Tissue culture experiments examined the dynamics of domain elongation in culture, using different proportions of co-cultured normal (dystrophin-positive) and dystrophic (dystrophin-negative) satellite cells (Kong and Anderson, 2001). (B) Micrograph showing expression of developmental myosin heavy chain (devMHC) in new myotubes formed over 4 days of regeneration following injury to normal muscle. (C) Micrograph showing laminin immunostaining surrounding skeletal muscle fibres. Laminin is one of the external matrix proteins that is complexed with the dystrophin-associated proteins that are either internal, transmembrane or linked with proteins inside the sarcolemma in normal muscle (Crawford et al., 2000; Ervasti and Campbell, 1993; Ferletta et al., 2003). In muscles affected by mutations in proteins of the dystrophin-associated protein complex, the expression of laminin is reduced; this is also noted in dystrophin-deficient muscle (Ferletta et al., 2003; Kanagawa et al., 2005; Kikkawa et al., 2004; Kim et al., 2004; Saito et al., 2005). Treatment with glucocorticoids increases the expression of laminin in mdx mouse skeletal muscle (Anderson et al., 2000). NOS-1 expression is also reduced secondary to dystrophin deficiency. There is significant alleviation of the dystrophic phenotype (in the mdx dystrophic mouse) by increasing the expression of NOS-1 in mdx mouse skeletal muscle (using transgenic approaches) and the use of a NOS substrate (L-arginine) to reduce the severity and progression of mdx mouse muscular dystrophy (Anderson, 2000; Anderson et al., 2005; Anderson and Vargas, 2003; Archer et al., 2006; Brenman et al., 1995; Brenman et al., 1996; Shiao et al., 2004; Tidball and Wehling-Henricks, 2004a; Tidball and Wehling-Henricks, 2004b; Wehling et al., 2001; Wehling-Henricks et al., 2005). (Original micrographs all ×140.)

Partridge, 2003; Rosenblatt et al., 1995). As stem cells, satellite cells can be considered as banked currency, anticipating the role in later growth and regenerative events.

Our laboratory has modelled myogenic fusion events using a co-culture system of normal myoblasts (satellite cell progeny) plated with dystrophin-deficient myoblasts isolated from muscles of mdx dystrophic mice. We observed that the domain of each myoblast nucleus enlarges during growth in culture, and that dystrophin diffuses along myotubes prior to the organization of a mature fibre cytoskeleton that is localized immediately inside the sarcolemma (Kong and Anderson, 2001).

Can a muscle run out of myogenic currency? It would seem the answer is yes. In muscular dystrophies, one concern about therapies that may increase muscle cell proliferation is that the replicative potential of satellite cells will become exhausted. Telomere shortening occurs on chromosomes as cells undergo numerous proliferative events, notable in DMD cells in culture (Cooper et al., 2003; Renault et al., 2002; Thornell et al., 2003), and it is well-established by modeling in cultures of muscle cells (derived from satellite cells) and single muscle fibres, that a gradual loss of proliferative capacity occurs with age and muscular dystrophy (Bockhold et al., 1998; Cooper et al., 2003; Jejurikar and Kuzon, Jr, 2003; Lagord et al., 1998; Renault et al., 2002). This 'bankruptcy' was demonstrated *in vivo* by experiments using repetitive muscle damage protocols that approached 50 events, exhausting the ability of satellite cells to proliferate and regenerate new muscle (Luz et al., 2002).

Satellite cells are not mere 'cuttings' that simply reproduce a muscle; as a heterogeneous population, the progeny will express a range of phenotypes. There is a consensus developing that anatomically defined satellite cells *per se* may be distinct from interstitial and circulating stem-like cells. Gene expression profiling in different stages of muscle development, growth, regeneration and aging has advanced this area tremendously. Some studies show a small subset of satellite cells that have more stem-like properties and may commit to alternate lineages (e.g. Asakura et al., 2002; Cao et al., 2003; Deasy et al., 2005; Jankowski and Huard, 2004; Sabourin and Rudnicki, 2000; Shefer et al., 2004). The observed level of heterogeneity in the satellite cell population may relate to differences in experimental design, the timing

and techniques of cell isolations and the proliferative (cell cycle) state of these cells at the time of isolation and subsequent observation.

Interestingly, in the context of gene profiling, there is very little information available regarding the networks or 'interactional groups' of genes expressed during conditions that inhibit myotube formation. This approach, somewhat the inverse to the characteristic format of asking what promotes regeneration and muscle growth, may provide very important clues to pathophysiology in neuromuscular disease.

(2) Satellite cells as a conveyance in skeletal muscle plasticity

The 'conveyance' role of satellite cells relates to their giving a muscle or fibre the 'access' to new or improved (adaptive) functions. Thus the conveyance provides a new 'generation' of progeny with a particular phenotype for adaptation, such as would be required to respond to changes in the severity of a disease, environmental toxicity, starvation, temperature change or weightlessness. This notion has been discussed in many reports (Blaivas and Carlson, 1991; Brooks and Faulkner, 1994; Carson and Always, 1996; Conboy et al., 2003; Conboy et al., 2005; Goldspink, 1998; Goldspink, 2004; Harridge, 2003; Karpati et al., 1990; McArdle et al., 2002; McGeachie et al., 1993; Thornell et al., 2003; Welle, 2002), and is a topic of some futuristic programming in the media.

The conveyance role is also displayed as the potential of satellite cells to adapt to demands in other tissues outside skeletal muscle, such as envisioned in tissue engineering and cardiomyoplasty. Satellite cells can serve to manufacture muscle as a patch or alternate contractile or non-contractile tissue (Muller-Ehmsen et al., 2002), or be genetically modified to make high levels of a hormone, non-muscle protein or a novel therapeutic protein (e.g. IGF-I). Experimental animal and pre-clinical human therapeutic trials are advancing the knowledge required to make these strategies more effective, accessible and safe.

One particular example is the utilization of satellite cells as a conveyance for the expression of dystrophin (in full or truncated form) to dystrophic muscles. Many experiments in cell therapy or myoblast transplantation employ myogenic cells derived from satellite cells that were amplified through tissue culture methods and exposure to vectors containing various gene constructs (reviewed elsewhere). The strategy is to deliver the protein missing from DMD muscle through the fusion of dystrophin-expressing myogenic cells with dystrophic myofibres. There is growing success in testing this modality of treatment (Chretien et al., 2005; Cossu and Mavilio, 2000; Cousins et al., 2004; Gussoni et al., 1999; Huard et al., 1994; Ikezawa et al., 2003; Jankowski and Huard, 2004; Li et al., 2005b; Liu et al., 2005; Partridge et al., 1989; Payne et al., 2005; Qu-Petersen et al., 2002).

Other experiments using transgenic technologies show the multi-potential nature of stem cells from a variety of source tissues (Cossu and Bianco, 2003; Sampaolesi et al., 2003). These strategies have brought stem cell therapy to the forefront of therapeutic muscle regeneration. The anticipation of cell therapy strategies has also encouraged study of non-invasive technologies such as magnetic resonance spectroscopy and imaging to monitor the success of cell engraftment or treatment (Cahill et al., 2004; Hoehn et al., 2002; McIntosh et al., 1998a; McIntosh et al., 1998b; McIntosh et al., 1998c). Again, of particular importance for therapies involving satellite cells as conveyors of muscle plasticity is the establishment of new satellite cell precursors (through some influences that induce quiescence) on the newly transformed host fibres. Detailed experiments have dissected the role of important environmental influences associated with tissue culture protocols and cell isolation (see above).

(3) Satellite cells also play a role as clues to the progress of muscle responses

Satellite cells serve a plastic role for research investigators and students, as 'clues' or markers of events in skeletal muscle that follow activation from G_0 or quiescence, into the cell cycle. The selection of particular genes to use as expression markers has been shown to affect the observed nature of currency and conveyance roles in satellite cell behaviour (Tamaki et al., 2002a; Tamaki et al., 2002b; Tamaki et al., 2003). Similar to studies of hematopoietic lineages and stem cells (Joseph and Morrison, 2005), experiments on satellite cells have attempted to isolate populations with homogeneous stem-like features from those with more differentiated characteristics. Culture conditions such as oxygenation (Csete et al., 2001; Csete, 2005) that otherwise seem innocuous and routine, can impose phenotypic changes even after brief exposure, for example changing the expression of a gene used to characterize the stem cell phenotype (Brunet et al., 2006). The delicacy of the muscle stem cell phenotype is revealed by observations that 6% oxygen (rather than the standard 20% oxygen used in routine tissue culture) increases satellite cell survival and the multi-potency of their currency (Csete et al., 2001). Interestingly, the distinctive behavioural characteristics of skeletal muscle stem cells in response to oxygenation are similar to those of neural stem cells (Csete, 2005; Studer et al., 2000).

Particular sets of genes denoting a stem-like phenotype have used sorting and cell purifications based on surface marker expression. Other experiments have profiled gene expression against hierarchies of genes (Boer et al., 2002; Fluck et al., 2005; Haslett et al., 2003; Nikawa et al., 2004; Porter et al., 2004; Seale et al., 2004a; Wu et al., 2003). Since the viability of the stem cells in their stem-like capacity is observed to decline after tissue dissociation and flow cytometry, fate-mapping experiments in other tissues have enabled investigators to follow the migration and multi-lineage differentiation of particular single cells [e.g. in the neural crest lineage (Bronner-Fraser and Fraser, 1988)]. The powerful *in ovo* approach to studying cell lineages in development has the potential to be achieved for single muscle fibre cultures observed over time, where the satellite cell-fibre complex within the basement membrane is retained similar to conditions *in vivo* (e.g. Shefer and Yablonka-Reuveni, 2005).

Single fibre studies have revealed clues about myogenesis and differentiation through the cascade of regulatory gene expression (e.g. Shefer et al., 2004; Shefer and Yablonka-Reuveni, 2005; Yablonka-Reuveni et al., 1999b; Yablonka-Reuveni and Rivera, 1994; Bischoff, 1986a; Bischoff, 1986b; Shefer and Yablonka-Reuveni, 2006; Yablonka-Reuveni and Anderson, 2005) and demonstrated the kinetics, symmetry or complexity of precursor cell division (e.g. Asakura et al., 2001; Beauchamp et al., 2000; Jones et al., 2005; Tamaki et al., 2003), the effects of deficient expression of particular proteins including syndecans, dystrophin and MyoD (Cornelison et al., 2000; Cornelison et al., 2004; Yablonka-Reuveni et al., 1999a), or changes with age or denervation (Bockhold et al., 1998; Kuschel et al., 1999; Yablonka-Reuveni et al., 1999b; Yablonka-Reuveni and Anderson, 2006). While full discussion of the properties of each of these proteins or conditions is outside the scope of this review, such experiments have satellite cells and their progeny under direct observation by immunostaining, autoradiography (Bischoff, 1986a; Bischoff, 1986b), *in situ* hybridization (including use of a Y-chromosome probe) plus combinations with histochemistry (Gussoni et al., 1999; Gussoni et al., 2002) or histochemistry and immunostaining (Cooper et al., 1999; Heslop et al., 2001; Kablar et al., 2003; Kassar-Duchossoy et al., 2005; Relaix et al., 2005). The applications of gene profiling have provided further, powerful approaches to studies of roles of various proteins in myogenesis and satellite cell activation (e.g. Seale et al. 2004a).

The exploration of myogenesis and particular treatment effects (from exposure to or expression of various ligands, molecules or drugs) have provided major clues to investigators on the nature of myogenesis and the immense plasticity of myogenic cell lineages in development and adaptation.

(4) Satellite cells as connectors between muscle and the environment

Satellite cells are positioned at the external aspect of muscle fibres and therefore form part of the direct environment of the fibre. Considering muscle, we often speak as if satellite cells are passive recipients of signals directed from muscle fibres or from the external environment. This is particularly true when considering satellite cells as quiescent on the fibre. However, since they are at least 'on call' for signals from the fibre or the further interstitial or circulating environment, there is no reason to exclude their potential to provide signals to other mononuclear cells (possibly attracting them to the site of an injury), other fibres, the blood stream, or to the fibre itself. Once activated, satellite cells and myogenic progeny release growth factors (FGF-2, VEGF and IGF-I) and muscle fibres express the relevant receptors. This means that fibre activity may be mediated in part by the products and signaling of muscle precursors, both activated (cycling) and those in an apparent quiescent state in the direct environment of fibres (intact or damaged), and studied *in vivo* or in culture systems. For example, growth factor production by muscle precursors affects consequent properties of differentiation by those precursors, as does the presence of the fiber in close proximity (e.g. Allen and Boxhorn, 1987; Allen and Boxhorn, 1989; Fan et al., 2002; Florini and Magri, 1989; Gal-Levi et al., 1998; Goel and Dey, 2002; Hameed et al., 2003; Husmann et al., 1996; Li et al., 2005a; Liou et al., 2002; Liu et al., 1998; Rabinovsky et al., 2003; Sheehan et al., 2000; Shefer and Yablonka-Reuveni, 2005; Yablonka-Reuveni and Anderson, 2006). It is also important to recall that growth factors such as VEGF have roles in muscle function, distinct from those in angiogenesis. This notion suggests an active role of satellite cells on fibres, and of satellite cell myogenic progeny between fibres, on muscle adaptation, including those signals that may originate from satellite cells that are described as mitotically and metabolically 'quiescent'. Furthermore, satellite cells and myogenic progeny have the capability to communicate with one another as well as with the nearby fibres, and the complexity of such a 'myogenic network' may have an impact on the eventual capacity for myofibre growth and formation, and satellite cell renewal. Considering a teleological train of thought, since satellite cells are close companions with fibres, it seems probable that they must engage in and require multi-way, cell–cell communication and feedback to be appropriately directed in plastic changes to the muscle phenotype. One might postulate that there are satellite cells that may signal to cells in the surrounding connective tissue, intramuscular vessels, nerves and beyond (e.g. *via* the blood stream).

The signal trafficking functions that pass in both directions between the fibre and surrounding extracellular matrix environment, are now in a field of intense interest that has evolved since the first discovery of dystrophin (Beggs et al., 1990; Darras et al., 1988; Hoffman et al., 1987; Koenig et al., 1988; Koenig and Kunkel, 1990; Kunkel and Hoffman, 1989). Laminin, integrins and fibronectin at the fibre surface affect fibre processes including calcium signaling and membrane recycling (e.g. Bansal et al., 2003; Bansal and Campbell, 2004; Kikkawa et al., 2004; Rando, 2001). Satellite cells may participate in this two-way connection between fibres and the environment. If we adopt the continuum model of stem cell regulation, then satellite cells could detect nearby signals and could contribute to the responses of the muscle fibre (e.g. Kami and Senba, 2005; Sachidanandan et al., 2002).

The role of adhesion is important in this perspective of satellite cells connecting the fibre to its environment. M-cadherin is produced by myogenic cells (Kaufmann et al., 1999) and deposited around the whole satellite cell (next to the basement membrane and in the cleft with the fibre). Studies of m-cadherin have contributed to defining the satellite cell population in development, regeneration and disease (Cooper et al., 1999; Cornelison and Wold, 1997; Irintchev et al., 1994; Tamaki et al., 2002b). The observation that a stretch stimulus applied to fibres in a model of normal physiological exercise induces satellite cell activation has shown that satellite cells have a role as physical or mechanical connectors to the environment (Anderson and Wozniak, 2004; Wozniak et al., 2003). New evidence that the release of the gaseous nitric oxide signaling molecule from multinucleated muscle cells is

rapidly triggered each time those cells are stretched in culture (A. C. Wozniak and J.E.A., unpublished data), demonstrates the integration of signaling between a fibre and the substrate environment that ultimately acts to activate satellite cells during normal muscle function.

(5) Satellite cells as colanders or environmental filters

Satellite cells are also likely to act as strainers or filters that can rectify or modulate particular signals. For instance, signals that are particularly important for long-term fibre adaptations may be read differently from signals essential for an effective regeneration. Satellite cells would need to make that distinction, and provide some form of feedback to fibres. This is a second instance where satellite cells may take an active role in directing the metabolic activity fibres or other nearby tissues. Regions of the fibre membrane have 'resident' satellite cells, and they may be either protected from or more sensitive to particular signals from the environment, than the regions without resident satellite cells. Somewhat oddly, the effect of HGF on cell mobilization in glomeruli of the kidney, a tissue that is exquisitely designed for active control of filtration, suggests there may be a tenuous analogy with satellite cells as a 'structural filter' (Miller et al., 1994). Signals critical to muscle may shift satellite cell functions toward quiescence and modulate the muscle response to alter metabolism rather than growth (Coppock et al., 2000). Such distinctions may explain differential responses of hypertrophy (enlarged cytoplasmic domains directed by myofibre nuclei) as compared to growth enabled by satellite cell proliferation and the contribution of additional cytoplasmic domains (by fusion). Likely there is a spectrum of responses that are marked by changes in the DNA-to-protein ratio in a fibre or muscle. Vascular, endothelial and interstitial signals may also be received differently by satellite cells than by the juxtaposed myofibres, and satellite cells may return distinct signals in response.

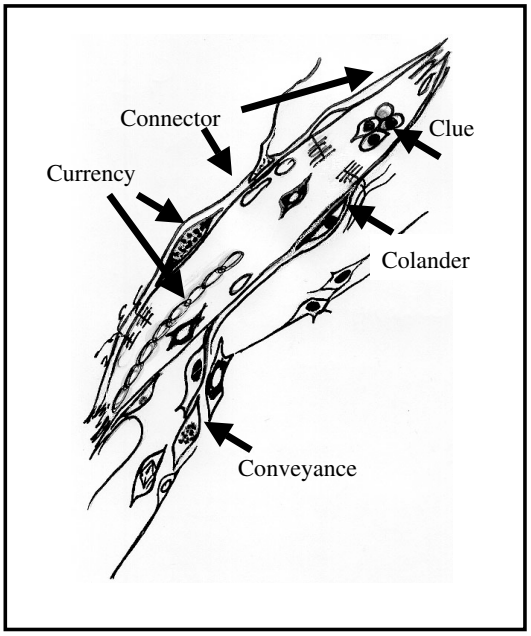

Fig. 7. A schematic of satellite cells on a regenerating fibre, depicting the roles of the satellite cell as currency to make new muscle; conveyance during migration and to bring therapeutic potential for new gene expression; clue to the processes of development, growth, regeneration and neuromuscular diseases; connector between fibres and signals in the environment; and as a colander to interpret and rectify signaling traffic while communicating with a fibre.

Satellite cell migration along the length and around the surface of fibres is further evidence that they are active participants in filtering the stimuli related to muscle plasticity. Satellite cells will actively travel between adjacent fibres, possibly with an intervening cell cycle that deposits a muscle precursor along the way. Relevant to muscular dystrophy, three types of experiments have demonstrated the spreading of dystrophin expression over time, since satellite cell progeny migrate after cell transplantation, exon-skipping therapy and in revertant fibres. The latter are dystrophin-expressing fibres as a result of somatic mutation in satellite cells and ensuing amplification in dystrophic muscle (Blaveri et al., 1999; Cousins et al., 2004; Lu et al., 2000; Partridge, 1998). Migratory capability is provided by key enzymes such as metalloproteinases and gelatinase, and especially interaction between hepatocyte growth factor and its receptor, c-met, as demonstrated by a growing number of detailed reports (Gal-Levi et al., 1998; Hartmann et al., 1992; Lewis et al., 2000; Lewis et al., 2001; Liou et al., 2002; Parr and Jiang, 2001; Sachidanandan et al., 2002; Sakkab et al., 2000; Tatsumi et al., 2001; Tatsumi et al., 2002). Stability of position is mediated by interactions of catenins with m-cadherin and other adhesion proteins (Kuch et al., 1997; Qu-Petersen et al., 2002). The relationship of muscle stem cells derived from vascular tissues to satellite cells, which typically are located close to the vasculature in a muscle, is not known (Cossu and Bianco, 2003; Galli et al., 2005; Goodell et al., 2001; Tavian et al., 2005). While satellite cells are reported to be present in higher numbers near neuromuscular and muscle-tendon junctions and vascular branches, any distinctive cell phenotypes in particular locations that have been suggested from the variations in morphological phenotype, have not been well defined by molecular studies.

Conclusion

The purpose of this review is to focus on and explore the roles of satellite cells in muscle plasticity, schematically presented in Fig. 7. Roles as currency, conveyance, clue, connector and colander each contribute to the complex companionship demonstrated by satellite cells and skeletal muscle fibres. Our perspective of the satellite cell 'world' defines how we might detect various indications of satellite cell function in skeletal muscle plasticity. If we take a systems approach (Csete and Doyle, 2002) to examine how satellite cell roles contribute to developing the plasticity, adaptability and remodelling capacity of muscle, we may find other functions revealed by alternative perspectives on structural and functional phenotypes.

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