Mini-Review

Myogenic Shape-Shifters

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A paper in this issue from the laboratory of Guilio Cossu (De Angelis et al., 1999) is of particular interest because it goes against the grain of what we think we know about two fundamental aspects of muscle biology: first, the embryonic origin of muscle cells; and, second, how damaged muscle repairs itself. Current models indicate that the nuclei in skeletal muscle myofibers originate from the embryonic somites, specifically from the cells located in the dorsal somite epithelium (Figs. 1 and 2). Adult skeletal muscle tissue is complex, consisting of multinucleated, contractile myofibers wrapped in connective tissue through which the blood vessels and nerves course (Fig. 3). Satellite cells are mononucleated cells that reside inside the basal lamina secreted by adult myofibers. When activated through injury, satellite cells initiate stem cell activity and gene expression that leads to the regeneration, replacement and/or hypertrophy of vertebrate skeletal muscle fibers (Bischoff, 1994; Yablonka-Reuveni, 1995; Cornelison and Wold, 1997). Evidence supporting the somitic origin of the nuclei that compose skeletal myofibers is substantial (recently reviewed in Ordahl et al., 1999). The source(s) of satellite cells, on the other hand, has never been unequivocally established (Armand et al., 1983). A recent paper that resulted from a collaboration that included the Cossu group, showed that blood-borne cells constituted a small but detectable source of myocytes during muscle regeneration in vivo (Ferrari et al., 1998). A finding that is consistent with previous predictions and reports of a class of multipotential stem cells within bone marrow and circulating blood (Owen, 1988; Caplan, 1991, 1994; Dennis and Caplan, 1996; Prockop, 1997; Dennis et al., 1999; Pittenger et al., 1999), and possibly, consistent with recent inclinations that the thymus may also be a source of myogenic stem cells (Wong et al., 1999).

Given that regenerative potential, De Angelis et al., 1999, sought to determine if such myogenic cells could be isolated from embryonic aorta endothelium, one of the first blood vessels to form in the early embryo (Figs. 1 and 2). Using an impressive combination of embryological, cell biological and transgenic technology, they show that isolated aorta does indeed give rise to small populations of myogenic cells. Moreover, when such endothelium is grafted directly into a muscle in which regeneration has been induced by injury, graft-derived myogenic cells can be found both in the injured muscle as well as in the muscle on the contralateral side, consistent with a blood-borne migratory capacity of such cells. The authors appropriately and carefully qualify their conclusions that blood-borne,

endothelial-derived cells can have myogenic capacity with two considerations: first, that such cells may contribute to, but not necessarily constitute all of, the regenerative capacity in adult muscle; and, second, that endothelial-derived cells have not been demonstrated to exist within the anatomically defined satellite cell compartment (Fig. 3). So, it remains to be determined if satellite cells are derived from the blood-borne cells analyzed by the Cossu group or if the latter represent an alternative source of myogenic repair cells.
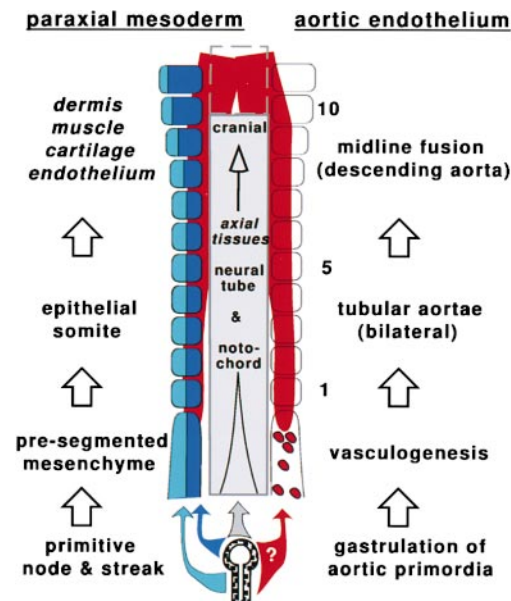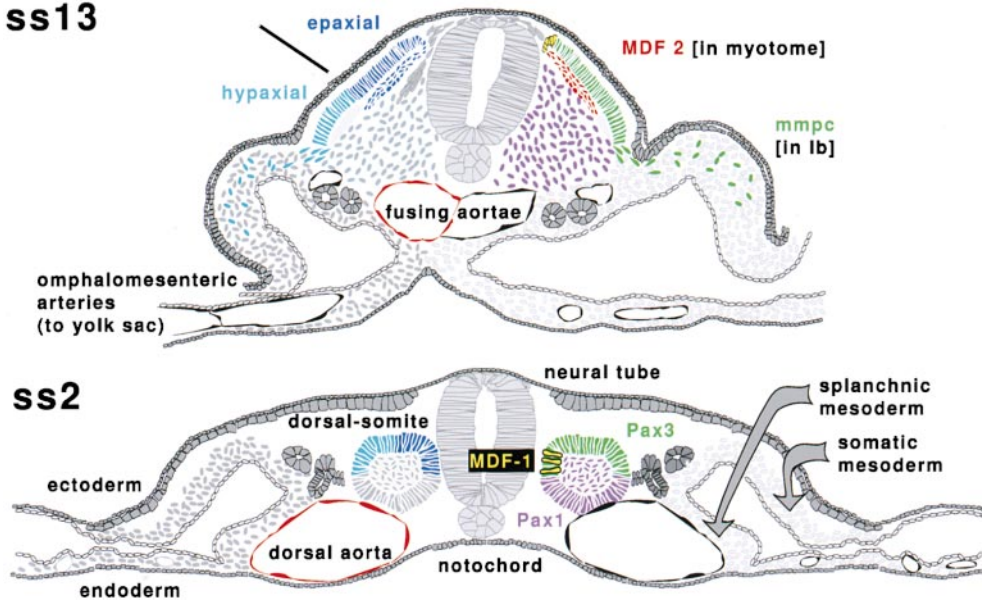

Figure 1. Aortic vasculogenesis and its relation to somite development. Schematic diagram of axial and paraxial development in vertebrate embryos summarizing the progressive changes in the development of somites (left) and aortic endothelium (right). Note that condensation of aortic primordia into a tubular aorta occurs approximately concomitant with somite epithelialization. Numbers on right indicate somite stages. (Left side) Medial (dark blue) and lateral (light blue) components of the paraxial mesoderm arise from distinct regions within the primitive node and streak and have distinct destinations during later development (see Fig. 2). At least four tissue types, including endothelium, are derived from somites (Pardanaud and Dieterlen-Lievre 1995; Wilting et al., 1995). (Right side) Aortic endothelial precursors coalesce beneath the presegmented paraxial mesoderm (Dieterlen-Lievre and Le Douarin, 1993; Jaffredo et al., 1998) to form bilateral aortic vessels that fuse to form a single aorta (the descending aorta in humans).

cell lineage | gene expression

Figure 2. Location of the first skeletal muscle precursor cells during early somite development. Schematic cross sections of chick embryos at the forelimb-level stages 2 and 13 of somite development (see Fig. 1). In each cross section, the left hand side highlights development of the aorta (red) as well as the lateral (light blue) and medial (dark blue) portions of the dorsal somite epithelium (dermomytome) while the right hand side highlights gene expression in the somite. MDF 1 and MDF 2 refer to two phases in the expression of myoD family genes in myoblast precursor cells and myocytes, respectively (see Ordahl et al., 1999). Migratory muscle progenitor cells (mmpc) leave the lateral portion of the dermomytome to enter the developing limb bud. Note that at early stages of development the aorta and somite are in close proximity and are closely adherent to one another (Pardanaud and Dieterlen-Lievre, 1995). Relative position and size of embryonic structures shown is adapted from (Hamilton, 1952; see also Ordahl et al., 1999).

With that in mind it is interesting to note that the origins of aortic endothelium and somites are not so far removed from one another during early development. Aortic precursor cells undergo vasculogenesis (a process distinct from angiogenesis) (Dieterlen-Lievre and Le Douarin, 1993, and references therein) immediately subjacent to the pre-somitic mesoderm, the unsegmented portion of the paraxial mesoderm (Fig. 1). Approximately concomitant with somite epithelialization, vasculogenic clusters fuse to form bilateral, patent dorsal aortae that are adherent to the somite ventral surface (Fig. 2). The close proximity in origins of these two lineages is also reflected in the fact that both are responsible for generation of endothelial cells (Pardanaud and Dieterlen-Lievre, 1995; Wilting et al., 1995). One hopes that this paper (De Angelis et al., 1999), along with previous studies from this group (Ferrari et al., 1998), will spur embryologists around the world to design experiments to fill in this specific gap in our understanding of the embryonic origin(s) of satellite cells and other adult cells with potential for muscle regenerative capacity.
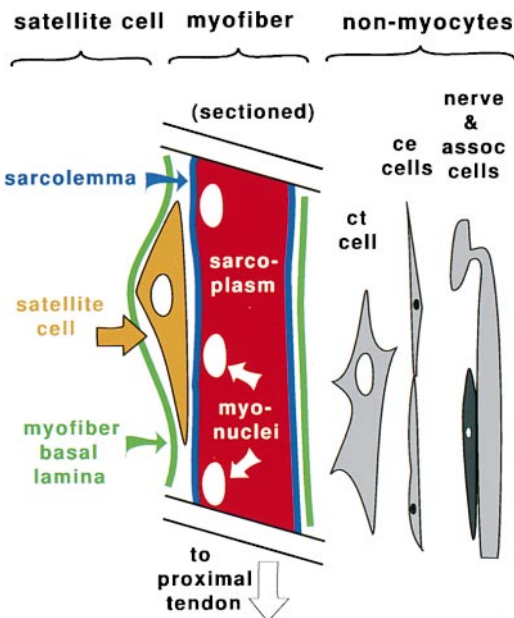
While the De Angelis paper provides grist for competing views of how stable tissues are built and maintained during vertebrate development, the outcome of that competition bodes well for an interested segment of the muscle field; patients for whom muscle repair or replacement is a medical necessity. Even assuming blood carries only a relatively small capacity for muscle regeneration, those cells possess a cardinal property that is essential if muscle replacement therapy is to become a reality: the ability to travel within the blood stream and then exit the bloodstream to colonize skeletal muscles. The ability to travel is present in migratory muscle precursor cells that populate the embryonic limb bud (see Fig. 2) but such capacity is no longer evident after grafting of replicating myoblasts (presumptive true satellite cells) isolated from muscle tissue and expanded in vitro (Gussoni et al., 1992, 1997). So, the

Figure 3. Cellular compartments of adult muscle tissue. Schematic diagram of a section of an adult muscle (center, red) with associated non-myocyte cell types (ct, cell-connective tissue cell; ce, cells-capillary endothelial cells; right hand side), and satellite cell (left hand side). Note that non-myocytes reside outside the basal lamina of the muscle fiber while satellite cells lie between the basal lamina and the sarcolemma of the myofiber.

biology and molecular genetics that we will learn about such blood-borne myogenic cells over the next few years may suggest strategies for either expanding their numbers or engineering their essential qualities into other myogenic cells. Either approach would constitute a potential win–win situation for research into myoblast transfer therapy for the treatment of muscle loss, through genetic diseases such as Duchenne's muscular dystrophy, or even non–life-threatening muscle loss that follows injury or exercise abuse.

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