
Development of Visceral Smooth Muscle

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The wide distribution of smooth muscle in the body is matched by patterns of development that differ in different organs. This review article deals with the origin, differentiation and growth of the smooth musculature of viscera. Only passing references will be made to the development of vascular musculature and to myoepithelial cells and myofibroblasts. The development of smooth muscle should be seen in the context of the special properties of this tissue. Smooth musculature is abundant (Table 1) and is found in all parts of the body; it performs with its contractions and its tone disparate functions, it grows while it is mechanically active, it is under the influence of local and systemic chemical factors and of mechanical factors, it produces the extracellular stroma (or matrix) that has the function of an intramuscular tendon and it adapts its growth and trophic condition to the functional demand imposed. The large assemblies of smooth muscle cells in the wall of viscera – as opposed to small groups or scattered muscle cells elsewhere in the body – undergo processes of development that consist not only in the cellular differentiation of a mesenchymal cell into a specialized contractile cell (cellular myogenesis), but also in the self-assembly and organization of the tissue, with the production of stroma and other features of supracellular organization (muscle differentiation).

1 Early Appearance of Smooth Muscles

The earliest morphological signs of the formation of a visceral smooth muscle are the elongation of the precursor cells and their grouping into a relatively dense cellular layer. The precursor cells arrange themselves parallel to each other, in contrast to the seemingly random orientation of the cells in the surrounding mesenchyme and of all the cells at an earlier stage. At the same time, the intercellular spaces of the primordial smooth muscle become narrower, a process related (it is not clear whether as a cause or as an effect) with the formation of more extensive intercellular contacts. In the chick, the process of elongation of mesenchymal cells, condensation of the cells and arrangement in a parallel array takes place at the end of the first week in ovo in the gizzard

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Table 1. Total amounts of smooth muscle in the human body. These are rough estimates of the amount (in weight) of smooth musculature in the human body. These guesses give a total of 1,000–1,600 g in total or 1.5–2.2% of body weight

Organ	Weight (g)
Bladder	30–60
Ureter, vesicles, vas	30–60
Uterus	200–400
Gut	700–1,000
Airways	50–100
Vessels	150–300
Skin	10–30
Diffuse musculature	50–100

and intestine (Bennett and Cobb 1969; Gabella 1989) and results in the formation of a layer of musculature, which, in the case of the intestine, is the circular layer. In the rat embryo, similar events start in the gut wall around day 15 or soon afterwards.

Development of a smooth muscle is here taken as synonymous with development of the component smooth muscle cells. What constitutes a smooth muscle cell, in early development, is partly a matter of definition: here the term is intended morphologically and is taken to refer to an elongated cell containing a substantial amount of bundled myofilaments. At earlier stages in their development these cells are here referred to as smooth muscle cell precursors, these cells being committed to develop into muscle cells and beginning to express biochemical markers of smooth muscle cells. In histochemical studies, markers such as smooth muscle actin and smooth muscle myosin heavy chain are taken as identifiers of a smooth muscle cell from its earliest stage of development. Thus, smooth muscle differentiation is defined as the onset of smooth muscle myosin heavy chain mRNA expression (Miano et al. 1994), or the expression of alpha-smooth muscle actin, but not yet of gamma smooth muscle actin (McHugh 1995) (see section 5). The term *anlage* or *anlagen* refers to the assembly or assemblies that these cells form. The timing and the mechanisms of the commitment of primordial cells to turn into muscle cells are unknown; it is unclear to what extent the commitment is reversible, or the extent to which precursor cells retain some pluripotency (see Sect. 9).

The appearance of precursor smooth muscle cells within an organ and their differentiation into muscle cells is a local process: it does not appear to involve a distant migration of cells or their redeployment, and its timing is organ specific. Also, it seems that it is not a focal process: for example, in the primitive small intestine, the precursor cells are distributed around the entire circumference of the wall and along its entire length (although it is possible that there is a gradient along the length of the gut, or across the thickness of the wall, see p. 9).

The path of differentiation of smooth, skeletal and cardiac muscles from mesenchymal precursors is determined long before any morphological signs appear. The apposition between cardiac and smooth musculature (in the vena cava) and that between striated and smooth musculature (in the oesophagus and urethra) are already observed in development: in every case, the two tissues are morphologically distinct, even when, as is usually the case, there is a considerable admixture of two cell types (which can be properly resolved only by electron microscopy). However, there are several histochemical and ultrastructural studies describing a process of transdifferentiation by which smooth muscles (or, rather, newly differentiated smooth muscle cells) differentiate into striated muscle fibres, in the chick embryo iris, in the rat urethra and in the mouse oesophagus (see p. 26).

The transition from precursor to smooth muscle cell involves marked changes in cell shape. The spatial orientation of these developing cells, within bundles, layers or the whole wall is well defined from the beginning and corresponds closely to that of the mature muscle cells in that particular organ. This early process of morphogenesis takes place at a time when there is very little extracellular materials and no collagen or other fibrils.

2 Timing of Smooth Muscle Development

The early development of smooth muscle varies in different organs. Only few accurate data are available, and the problem is often compounded by difficulty in the timing or staging of embryos and in the definition of early stages of development. For example, the 7-day-old embryos of Ko et al. (1996) were at the same Hamburger-and-Hamilton stage (26–28) as the 5-day-old embryos of Hirai and Hirabayashi (1983) and Paul et al. (1994).

In general, visceral smooth muscles are well differentiated soon after birth and are already similar to those of the adult; in contrast, vascular muscles (which had been the first to appear during embryonic life) undergo marked structural changes postnatally, a characteristic probably related to the occurrence of haemodynamic changes and to the late formation of conspicuous extracellular materials in large vessels. For example, incorporation of valin into elastic fibres of the media of the mouse aorta, as studied by autoradiography, continues up to 4 weeks after birth (Davis 1993) and, in the rat, the volume of the extracellular material in the media of the aorta increases tenfold from birth to day 11 (Olivetti et al. 1980). As to visceral muscles, there are clear differences in the time at which they appear in different viscera and probably also in their rate of growth. The intestinal musculature is more differentiated at birth than that of the vas deferens; the muscularis mucosae appears last in the wall of the intestine. Generally, it seems that the circular musculature develops earlier than the longitudinal musculature. Even in blood vessels there are marked difference in the timing of development; for example, the musculature of the coronary artery of the chick matures in advance of that of the aorta (Hood and

Rosenquist 1992). A special case is that of the chick amnion, in which a one-cell-thick layer of smooth musculature develops outside the embryo and reaches morphological maturity around the tenth day of incubation (Evans and Evans 1964), which is well in advance of any muscle of the embryo. The musculature of the amnion is contractile, producing some movement of the amniotic fluid at a time when the embryo has no spontaneous motility. (The early regression of the amnion musculature from the end of the second week is still unexplored.)

In chick embryos, smooth muscle appears in the gizzard (muscular stomach) at about day 7 (Bennett and Cobb 1969). Soon after that time a circular muscle layer becomes recognizable in the small intestine. A special layer of muscle cells at the inner border of the circular layer becomes recognizable at around day 11. A longitudinal muscle layer beneath the serosa is seen from around day 13. An inner longitudinal muscle layer (similar to a muscularis mucosae) beneath the mucosa becomes recognizable at around day 15 (Gabella 1992) and, at this stage, all the layers of the mature intestinal wall are recognizable and in place. The musculature of the rectum develops with a similar pattern (although there is no special layer of circular musculature), but some 2 days later than in the small intestine.

In the guinea-pig ileum the first muscle cells are seen in the presumptive circular layer from 25 days of gestation (and not at 20 days), and in the longitudinal muscle by day 32; between these two stages the myenteric plexus is formed, lying by the outer aspect of the circular muscle (Gershon et al. 1981). In another study of the guinea-pig ileum, a primordial circular musculature was found along the entire length of the small intestine in embryos of 8 mm CR length (Fig. 1A–C); at this stage, there was no musculature in the wall of the large intestine (Fig. 1D). Later in gestation, a longitudinal muscle appears (Fig. 2A,B) and, closer to term, a special layer of circular musculature and a muscularis mucosae becomes apparent (Fig. 2C,D). In the colon of 4-week-old dog embryos (mid-gestation) a circular muscle layer ($\sim 30\mu\text{m}$ thick) and a minute longitudinal layer ($\sim 9\mu\text{m}$ thick) were already visible (Ward and Torihashi 1995).

In the uterus of the swine at birth, a condensation of roundish cells into a subserosal layer is the primordial myometrium (Bal and Getty 1970). Muscle cells, elongated in a circular direction, are seen only from the age of 2 weeks and a longitudinal musculature from the age of 1 month. The process is more advanced in the body of the uterus than in the horns (Bal and Getty 1970). In the human uterus, primitive muscle cells (identified by the presence of myofilaments) are seen at 18 weeks of gestation (CR length 145 mm; and not at week 16 or earlier) in a cell layer close to the serosa; close to the mucosa the mesenchymal cells begin to acquire the appearance of fibroblasts. The distinction between the two regions of the wall is clear, and one gives rise to the myometrium the other to the endometrial stroma (Konishi et al. 1984). Differentiation of the myometrial muscle cells is more advanced at 31 weeks, but it is markedly less than in the bladder detrusor examined in the same study

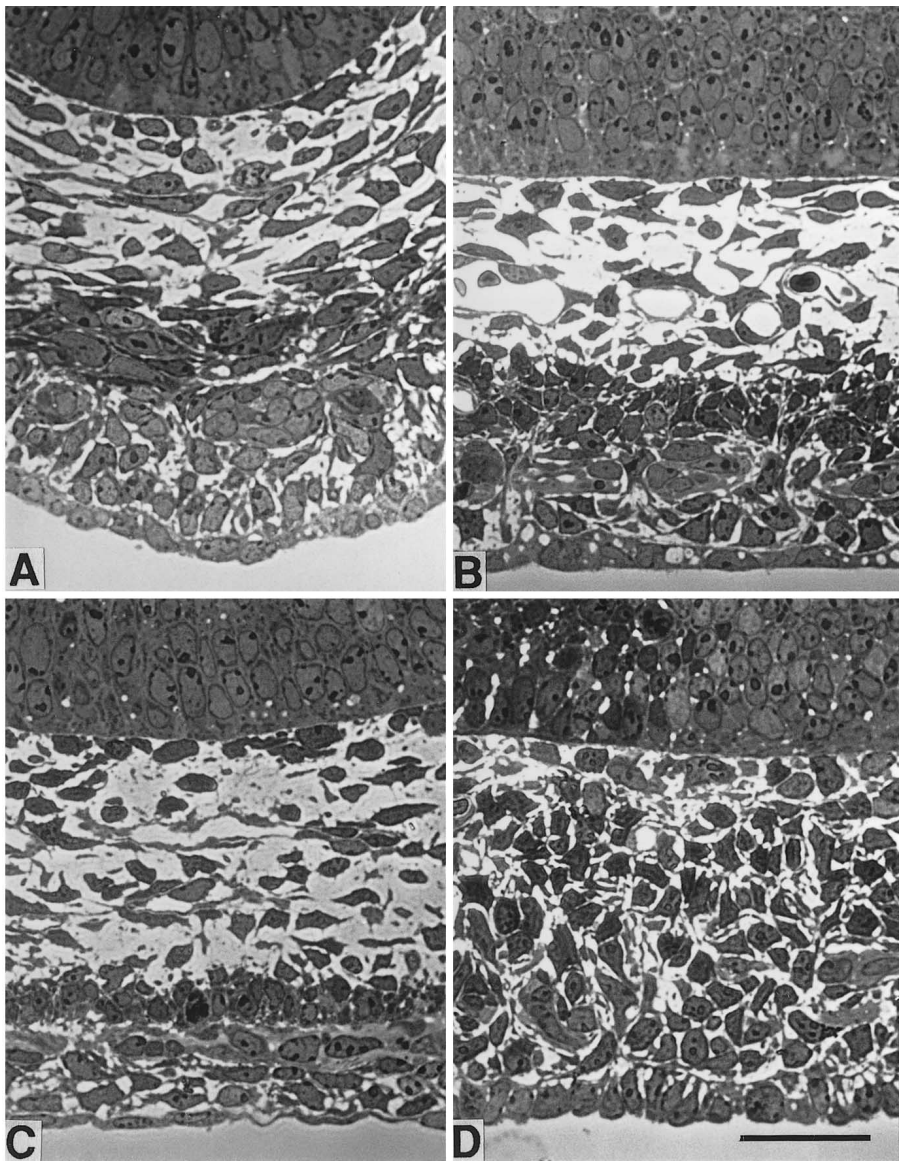


Fig. 1. Developing intestine from guinea-pigs in early gestation examined by light microscopy. **A** 8-mm CR embryo, transverse section of ileum. **B** 8-mm CR embryo, longitudinal section of ileum. **C** 8-mm CR embryo, longitudinal section of duodenum. **D** 8-mm CR embryo, longitudinal section of rectum. Calibration bar 30µm



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