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Review

Multiple roles of timing in somite formation

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ABSTRACT

During development, vertebrate embryos produce serially repeated elements, the somites, on each side of the midline. These generate the vertebral column, skeletal musculature and dermis. They form sequentially, one pair at a time, from mesenchymal tissue near the tail. Somite development is a complex process. The embryo must control the number, size, and timing of somite formation, their subdivision into functional regions along three axes, regional identity such that somites develop in a region-specific way, and interactions with neighbouring tissues that coordinate them with nearby structures. Here we discuss many timing-related mechanisms that contribute to set up the spatial pattern.

Contents

1. Introduction

During development of vertebrate embryos, a series of repeated elements, called somites, is laid down on either side of the main axis of the body (neural tube and notochord) (for reviews see Refs. [1–4]). In amniotes (reptiles, birds, mammals) each somite is initially an epithelial sphere, composed of about 1000-2000 cells, arranged around a central lumen (which contains some mesenchymal cells and extracellular matrix) and surrounded by a basal lamina of fibronectin and other extracellular matrix materials. Some hours after its formation, the cells in the ventromedial part of each somite (adjacent to the notochord and ventral neural tube) become mesenchymal again – this part of the somite is the sclerotome, whose cells will contribute to the vertebral column. The dorsolateral part (adjacent to the surface ectoderm) remains epithelial for longer – this is the dermomyotome, which eventually splits further into the dermatome most dorsally (still epithelial), which will contribute to the dermis of the trunk, and the myotome which will generate the epaxial muscles that extend and flex the vertebral column. The hypaxial musculature arises from cells at

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the ventrolateral edge of the dermomyotome, which migrate to invade the limbs and flank body wall. The sclerotomal contribution to the vertebral column generates the vertebral centra, the neural arches and associated spinous and transverse processes (including the proximal part of the ribs), as well as the annulus fibrosus of the intervertebral discs (which arises mainly from the mesenchymal cells that once resided in the somitic lumen [5,6]). The nucleus pulposus (centre) of the inter-vertebral discs derives mainly from the notochord. Somite cells also generate inter-vertebral blood vessels [7–9].

The complexity of the pattern of somites is much greater than is apparent at first sight. Each somite is further subdivided into molecularly distinct rostral and caudal halves and this property is crucial both for dictating the segmental pattern of components of the peripheral nervous system (the motor nerves and neural crest derivatives including the autonomic ganglia, dorsal root ganglia and their central and peripheral projections), which are all confined to the rostral half [10–12], and for maintaining the segmental pattern by preventing mixing of cells between adjacent somites [13]. These properties later allow the process of "resegmentation" by which each vertebral centrum is formed from the caudal half of one sclerotome and the rostral half of the next sclerotome [14]. Moreover, somites are not identical along the length of the body axis – they have characteristic shapes and other properties in different regions (occipital, cervical, thoracic, lumbar, etc.). These properties are encoded by expression of combinations of Hox genes (see doi:10.1016/j.semcdb.2015.06.001, in this issue). Somites are also subdivided into a medial and a lateral half – these arise from distinct regions of the anterior primitive streak during gastrulation [15,16] – after their formation, each somite rotates by about 45° so that the original North pole is relocated more laterally, and such that the original lateral half contributes mainly to the hypaxial musculature whereas the medial half generates the myotome and epaxial muscles (see above) [17]. The medial–lateral subdivision is further reinforced by medial signals from the notochord (Sonic hedgehog and probably Noggin) and dorsolateral signals from the surface ectoderm (BMP) [18,19].

Although we now know a considerable amount about the signals and responses that set up the gross subdivisions of the somites and establish the various cell fates as well as regional properties, it is perhaps surprising that we know comparatively little about the mechanisms responsible for controlling the gross pattern including the total number of somites, the size of each individual somite (which varies somewhat along the axis), or what regulates the timing of formation of each somite so that it is so precise and synchronous on both sides of the embryo, or how somites acquire their regional addresses (Hox code) along the length of the body axis. It is clear that all of these aspects involve the conversion of temporal information into spatial patterns, and therefore that timing must be involved in several different ways. Several models have been put forward to explain different aspects of somite formation, including the clock-and-wavefront model [20] and several newer versions of it [4,21–27], the cell cycle model [28–30], the delayed coupling model (multiple interacting oscillators) [31], clock-and-induction [32] and clock-and-trail models [33], and a traction-based model [34]. However to date, none of these fully explains all aspects of somite patterning. This review briefly draws attention to several aspects of somite formation that involve timing issues that appear to have been overlooked by much of the current literature. We will focus mainly on the chick embryo but make some reference to other model systems.

2. A conveyor-belt of cells: age order within the presomitic mesoderm

An important feature of somitogenesis is that it proceeds in head to tail order, separating cohorts of cells into somites in a sequential, orderly manner. In the chick, one somite forms every 90 min or so; this varies somewhat among different vertebrates: faster in teleost and anuran amphibian embryos and slower in most mammals. Each somite condenses into an epithelial ball from the bilateral strips of paraxial presomitic mesoderm (PSM) that lie caudal to the forming somites, where most of the cells have mesenchymal morphology. In turn, cells enter into the PSM from its caudal end, coming from the tip of the primitive streak including part of Hensen's node. In chick embryos, from the time a new cell enters the PSM at its caudal end to the time it becomes part of a formed somite corresponds approximately to 18–20 h, during which interval 12–13 somites will have formed from cells that were located at a more advanced (cranial) position when the cell entered the PSM [28,29]. A further 8–10 h (about 6 somites worth) then elapse before the newly-formed epithelial somite separates into dermomyotome dorsally and sclerotome ventromedially. Fig. 1 shows a Scanning Electron Micrograph of a stage 12 chick embryo

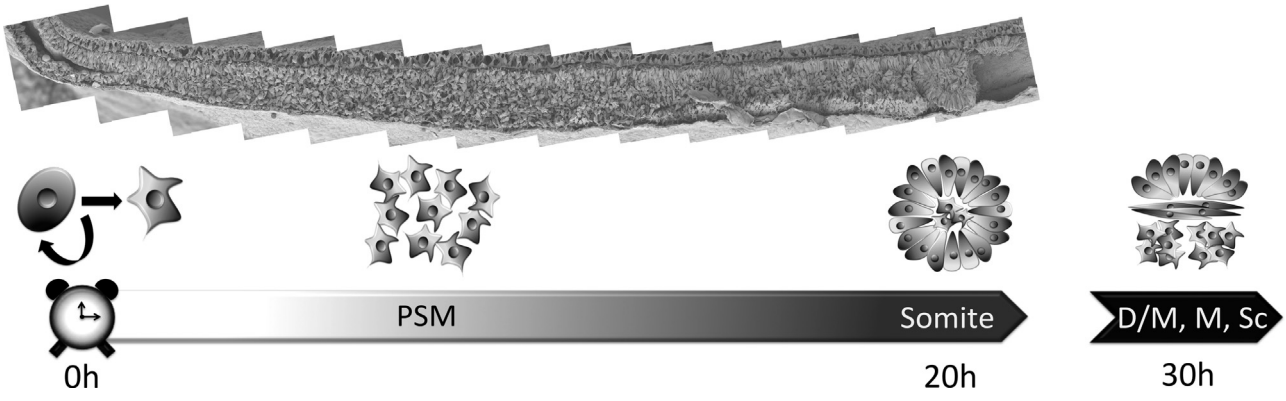

Fig. 1. The upper part of the figure shows a Scanning Electron Micrograph (SEM) of an embryo at the 15 somite stage (stage HH12), fractured parallel to the head–tail axis, along the length of the PSM. The section covers the PSM from the tail (left) to the most recently formed somite. Below this, the diagrams schematise the various cell states and morphologies that cells pass through as they progress through the process of somite development. Cells (at least some of them derived from self-renewing stem cells at the primitive streak) enter the caudal PSM (time "0 h" in the time scale below), where they have a mesenchymal morphology. Their sojourn in the PSM lasts about 20 h, and they exit as a newly-formed somite with epithelial structure (surrounding a central core of cells that remains mesenchymal). Later (30 h, equivalent to about 7 somites) the somite subdivides into the dorsally located epithelial dermomyotome (D/M), the ventrally located mesenchymal sclerotome (Sc), and a myotome (M) made up of an elongated stack of cells. The dermomyotome will give rise to dermis and hypaxial muscle, the myotome will generate epaxial muscles of the trunk and the sclerotome will generate the vertebrae and contribute to intersegmental blood vessels.