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Review

Early development of the vertebral column

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ABSTRACT

The segmental organization of the vertebrate body is most obviously visible in the vertebral column, which consists of a series of vertebral bones and interconnecting joints and ligaments. During embryogenesis, the vertebral column derives from the somites, which are the primary segments of the embryonic paraxial mesoderm. Anatomical, cellular and molecular aspects of vertebral column development have been of interest to developmental biologists for more than 150 years. This review briefly summarizes the present knowledge on early steps of vertebral column development in amniotes, starting from sclerotome formation and leading to the establishment of the anatomical bauplan of the spine composed of vertebral bodies, vertebral arches, intervertebral discs and ribs, and their specific axial identities along the body axis.

Contents

1. Introduction

The vertebral column is a metameric array of tightly interconnected skeletal elements, the vertebrae. It constitutes the supportive yet flexible backbone of all higher chordates, which are therefore systematically grouped as vertebrates. Between

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vertebrate taxa, the morphology of the vertebral elements, which can be of cartilaginous or bony nature, is very diverse. Whereas in amniotes, a vertebral segment consist essentially of a vertebral body (centrum) and a vertebral arch with the associated vertebral processes and joints, vertebrae in anamniotes can be more complex, showing variable numbers of centrae per segment, and next to a dorsal (neural) arch a ventral (hemal) arch may exist [1,2]. In this review, I will give a brief overview on the present understanding of how the vertebral column develops during embryogenesis. I will focus on amniote development, reviewing data mainly from the mouse and chicken embryo. Readers with interest in anamniote vertebral development are referred to previous summaries [1–3].

2. Sclerotome development

During embryogenesis, the vertebral column forms from somites, which are primary segments sculpted from the presomitic paraxial mesoderm in a process called somitogenesis [4]. In the course of craniocaudal elongation of the body axis, somites are added like pearls on a thread at either side of the neural tube and notochord, starting at occipital and ending at caudal levels. The newly formed somites are epithelial spheres, but soon the ventral cells undergo epithelia-mesenchymal transition (EMT) to form the mesenchymal sclerotome, whereas the dorsal half forms an epithelial sheet, the dermomyotome, from which the dermis of the back and the myotomal trunk muscle anlagen arise [5] (Fig. 1). The mesenchymal sclerotome cells, in contrast, form among other tissues the vertebral column and the ribs [6,7]. Prior to cartilaginous differentiation, the sclerotomal mesenchyme proliferates and migrates to ensheath the notochord and the neural tube and to extent laterally into the somatopleure, thus forming the anlagen of the vertebral bodies, vertebral arches and ribs, respectively. Accordingly, sclerotome formation is the starting point of overt vertebral column development, and is common to all vertebrate taxa including ancestral forms like jawless hagfish [8,9], notwithstanding the great variability of vertebral forms in this subphylum.

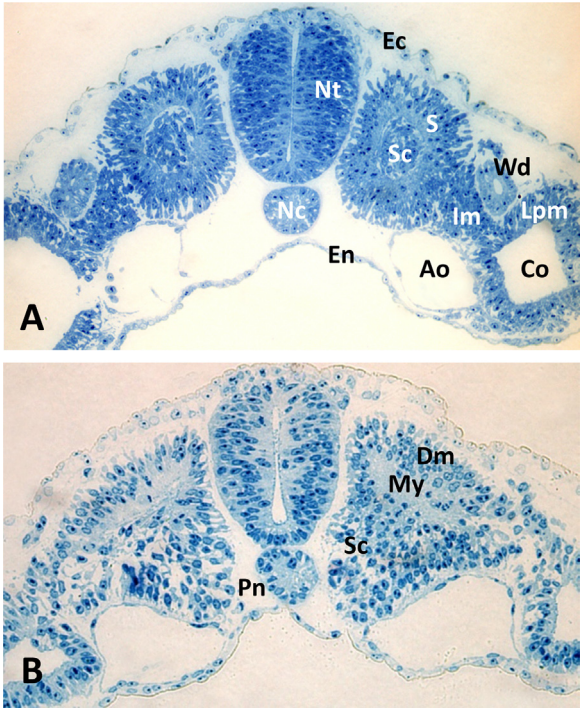

Fig. 1. Early steps of somite maturation. (A) As a result of somitogenesis, the newly formed somites of somite stages I–III are epithelial spheres with a central cavity, the somitocoel, which is filled with mesenchymal cells. At these stages, specification of the mediolateral and dorsoventral polarity of the somite occurs upon signaling from the neighboring neural tube, notochord, intermediate and lateral plate mesoderm. Transversal semithin section, HH-stage 15, somite II. Ao Aorta, Ec Ectoderm, En Entoderm, Co Coelomic cavity, Im Intermediate mesoderm, Lpm lateral plate mesoderm, Nc Notochord, Nt Neural tube, S Epithelial somite, Sc Somitocoel. (B) After somite polarity has been established, the somite is divided into three major compartments, the dermomyotome, myotome and sclerotome. Transversal semithin section, HH-stage 11, somite X. Dm, Dermomyotome, My, Myotome, Pn, Perinotochordal space, Sc Sclerotome.

2.1. Sclerotome formation

The two most recently formed somites (somite stages I and II in the staging system of Christ and Ordahl [10]) are still naïve with respect to dorsoventral polarity [11–13]. Only starting at somite stage III, the fate of the ventral somite half is determined to develop into the sclerotome. At this stage, the somite is still a homogeneous epithelial sphere, but the prospective sclerotome cells start to express the paired-box transcription factor *Pax1* [14], which is therefore frequently used as a molecular marker of the sclerotomal somite compartment (Fig. 2). *Pax1* expression is induced by signals from the notochord and the floor plate of the neural tube [15]. Although it is widely accepted that Shh originating in the axial organs is an inducer of *Pax1* expression via the downstream transcription factors Gli2 and Gli3 [16,17], the finding that Shh(−/−) mice still show transient *Pax1* expression [18] indicates that other early inducers are involved. The BMP antagonists Noggin, which is secreted from the notochord, and Follistatin and Gremlin in the paraxial mesoderm, are thought to allow for Pax1 mediated sclerotome development in the ventromedial somites as they inhibit the lateralizing BMP4 signals from the intermediate and lateral plate mesoderm [19,20]. Along the dorsoventral axis, sclerotome-promoting ventral Shh signals from the notochord and floor plate are competing with sclerotome-inhibiting dorsal Wnt signals from the roof plate and surface ectoderm. Thus, high levels of Shh but low levels of Wnts are required to determine sclerotomal fates as opposed to dermomyotomal fates and vice versa [21,22]. With little delay to *Pax1*, from somite stage IV/V on, another paired-box gene, *Pax9*, is expressed throughout the sclerotome [23]. Pax1 and Pax9, together with the sclerotomal homeobox proteins Meox1 and 2, activate the transcription factor Nkx3.2, which is synonymous with Bapx1 [24–26]. Nkx3.2 is a transcriptional repressor which triggers chondrogenic differentiation in sclerotomal cells [27]. While sclerotome development is thus initiated on a molecular level, the ventral somite cells downregulate *N-cadherin* expression [28] and undergo EMT to form a mesenchymal cell population, thus morphologically discriminating the sclerotome from the epithelial dermomyotome. This EMT seems to occur independent of Pax1/9 and Nkx3.2 activity, as the respective mutant mouse embryos show normal onset of EMT [29,30]. Within the mesenchymal sclerotome, *Pax1* is subsequently downregulated in cells which undergo chondrogenesis, and only maintained in the mesenchymal anlagen of the intervertebral discs and the perichondrium of the vertebral bodies [31,32]. Thus, even though Pax1 is required to initially trigger chondrogenesis in the early sclerotome [25], it is an inhibitor of chondrocyte differentiation and mutually exclusive to promoters of cartilage formation like e.g. Nkx3.2, Sox9, and Ihh which are expressed in the differentiating sclerotome [32].

2.2. Sclerotome compartmentalization

In accordance with the different portions of the vertebral elements to be formed, the sclerotomal mesenchyme needs to acquire polarity along the body axes and to divide into distinct compartments. According to Christ et al. [6], the early sclerotome can be divided into a ventral, central, dorsal and lateral compartment, which will form the vertebral body, pedicle, neural arch and rib