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Review

Bone development

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ABSTRACT

The development of the vertebrate skeleton reflects its evolutionary history. Cartilage formation came before biomineralization and a head skeleton evolved before the formation of axial and appendicular skeletal structures. This review describes the processes that result in endochondral and intramembranous ossification, the important roles of growth and transcription factors, and the consequences of mutations in some of the genes involved. Following a summary of the origin of cartilage, muscle, and tendon cell lineages in the axial skeleton, we discuss the role of muscle forces in the formation of skeletal architecture and assembly of musculoskeletal functional units. Finally, ontogenetic patterning of bones in response to mechanical loading is reviewed.
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Contents

Introduction

The development of the vertebrate skeleton reflects its evolutionary history in that different parts utilize different cellular sources and differentiation mechanisms for their formation [21,50]. The development of cranial bones can be traced back to the evolution of Craniates in the early Cambrian period, when chordates evolved a head with a brain, eyes and other sensory organs protected by a cartilaginous non-mineralized skull [68]. In the late Cambrian, Euconodont fossils show mineralization of tooth-like structures and a cartilage head skeleton, but no axial skeleton. Cartilage formation appears therefore to predate biomineralization, and a head skeleton evolved before axial and appendicular skeletal elements. The axial skeleton evolved first as a structure of unmineralized cartilage around the notochord that later (after lampreys diverged from other vertebrates) became mineralized and replaced by bone. Evolution of gnathostomes with jaws, a shoulder girdle and two paired sets of appendages represented a breakthrough in the mid-Ordovician period.

Endochondral and intramembranous ossification

Given the stepwise progress of skeletal evolution over millions of years it is not surprising that different cell lineages contribute to

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different parts of the mammalian skeleton. Neural crest cells from the dorsal margins of the closing neural tube migrate into the anterior region of the skull, giving rise to dentin of teeth and the connective tissue and some of the bones and cartilages of the face and anterior skull. Prechordal mesodermal cells produce cartilages and bones in the posterior part of the skull. Paraxial mesoderm (somites) is the cellular source of the axial skeleton, whereas lateral plate mesodermal cells form the appendicular skeleton (Fig. 1). The initiation of skeletogenesis starts with migration of mesenchymal cells derived from these embryonic lineages to the sites of the future bones. Here they form condensations of high cellular density that outline the shape and size of the future bones, i.e. the anatomic identity of the skeletal element is predetermined [70]. Within the condensations, the mesenchymal cells either differentiate into chondrocytes and form cartilage models (anlagen) of the future bones (endochondral bone formation) or differentiate into osteoblasts to directly form bone (intramembranous bone formation). Endochondral bone formation occurs in the skull base and the posterior part of the skull, the axial skeleton and the appendicular skeleton. Intramembranous bone formation takes place in the membranous neuro- and viscerocranium and in part of the clavicle.

The replacement of cartilage with mineralized bone in endochondral bones (endochondral ossification) is a complex process, triggered by differentiation of proliferating chondrocytes in the center of cartilage anlagen to a non-proliferative hypertrophic state. This is followed by invasion of osteoblast progenitors, osteoclasts, blood vessel endothelial cells and hematopoietic cells from the perichondrium into the hypertrophic cartilage. The hypertrophic cartilage is resorbed, the incoming osteoblast progenitors differentiate into trabecular bone-forming osteoblasts, and hematopoietic and endothelial cells establish the bone marrow in what becomes the primary ossification center [34]. Osteoblast progenitors in the perichondrium differentiate into osteoblasts that deposit cortical bone around the cartilage anlage. As the fetus grows, the primary ossification center expands and secondary ossification centers form in one or both ends of the developing bone. This results in the development of epiphyseal growth plate cartilage, responsible for the longitudinal growth of bones [22,28]. Within growth plates, chondrocytes are organized into structural and functional zones, each with distinct gene expression patterns [43]. Small and relatively inactive cells are located in the reserve zone close to the secondary ossification center, whereas proliferating chondrocytes are present in the adjacent proliferative zone. These cells undergo clonal expansion and align themselves into columns parallel to the direction of longitudinal growth. As the cells enter the hypertrophic zone, they stop proliferating and may undergo apoptosis. Recent data suggest that hypertrophic cells are not all undergoing apoptosis, but may also become osteoblasts [65]. With age, the growth plates get thinner and are eventually replaced by bone at various times after puberty in humans.

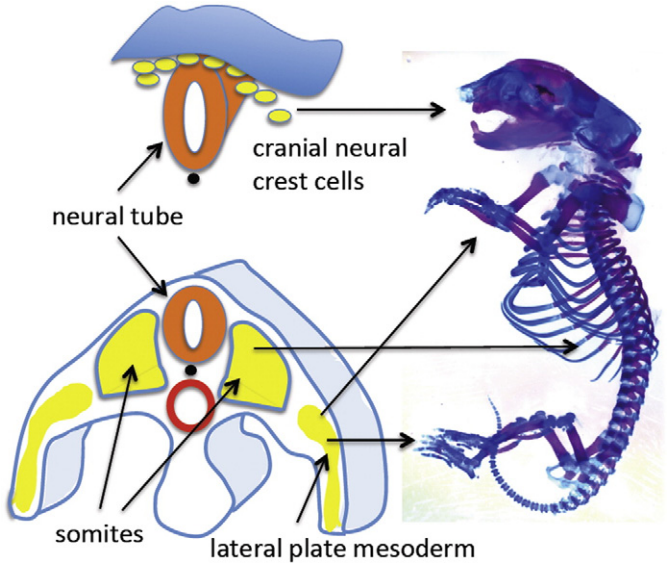

Fig. 1. Diagrams illustrating the contributions of cranial neural crest cells, somite-derived cells and lateral plate mesodermal cells to the craniofacial, axial and appendicular parts of the mouse skeleton. The notochord under the neural tube (top part) and between the neural tube and the aorta (red ring; bottom part) is indicated by a black dot.

Local and systemic factors regulate proliferation, differentiation and apoptosis of growth plate chondrocytes. A local factor, Indian hedgehog (Ihh), is produced by prehypertrophic chondrocytes, promotes hypertrophy and stimulates proliferation of chondrocytes in the proliferative zone [36]. It also stimulates osteoblast differentiation and synthesis of parathyroid hormone-related peptide (PTHrP) in the perichondrium. In turn, PTHrP inhibits the transition of proliferative chondrocytes to prehypertrophic, Indian hedgehog-expressing cells. This establishes a negative feed-back loop that controls the size and activity of the proliferative zone in the growth plate and couples cortical bone formation to the longitudinal growth of the bone. Synthesized in the perichondrium, fibroblast growth factor 18 (Fgf18) acts as a negative regulator of chondrocyte proliferation by activating fibroblast growth factor receptor 3 (Fgfr3) signaling in proliferating and prehypertrophic chondrocytes [17]. Proliferation is also controlled by growth hormone and insulin-like growth factor 1 (IGF-1) [2,49]. Deficiencies or activating gene mutations in these factors result in phenotypes with reduced growth and dwarfism without effects on bone shape or structure.

Regulation of skeletal patterning and differentiation of chondrocytes and osteoblasts

During evolution many genes and associated signaling pathways have been recruited as regulators of the phylogenetic patterning of the vertebrate skeleton [21,28,50]. The use of genetic approaches in mice and studies of the genetic basis of hereditary skeletal diseases in humans have been important for their identification [44,45,67]. A number of skeletal dysplasias are associated with defects in production or functionality of cartilage and bone matrix; others cause defects in differentiation or function of chondrocytes, osteoblasts and osteoclasts. This results in compromised skeletal growth or too much or too little cartilage and bone. Conditions known as dysostoses affect particular skeletal elements and not skeletal tissues in general. They include mutations in patterning genes that affect the size and shape of specific bones. The phenotypic consequences of such defects can develop at different stages, such as during mesenchymal condensations, differentiation into proliferative chondrocytes or maturation into hypertrophic chondrocytes. Studies of such disorders have identified transcription factors that are crucial for patterning and formation of cartilage and bone, including members of the homeobox (*Hox*) and paired-box (*Pax*) families (for review see [18,29,37,44]). Mutations in *HOXD13* result in shortening of the phalanges and/or the metacarpals (brachydactyly; OMIM 113200 and 113300 and brachydactyly-syndactyly; OMIM 610713 syndromes) or syndactyly with or without polydactyly (syndactyly; OMIM 186300 and synpolydactyly; OMIM 186000) [20,47]. Mutations in *HOXA13* are associated with unusually short great toes and abnormal thumbs (hand–foot–genital syndrome; OMIM 140000) [42]. Mutations in *PAX3* may result in a musculoskeletal phenotype (craniofacial-deafness-hand syndrome; OMIM 122880) in which all fingers show ulnar deviation as a result of a muscle defect, combined with sensorineural hearing loss, underdeveloped or absent nasal bones, hypertelorism and a small upper jaw, and permanently bent third, fourth and fifth fingers in some patients. *PAX3* mutations can also cause abnormalities in the upper limbs, associated with hearing loss and changes in pigmentation (Type III Waardenburg syndrome; OMIM 148820) [61,69].

Members of the transforming growth factor beta (TGF-β) superfamily, such as growth and differentiation factors (GDFs) and bone