# SECTION 1

## Bones of the oral-dental and craniofacial complex

# 1

# Embryology of craniofacial bones

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In this chapter, we provide a general overview of embryological events pertinent to the development of the bony structures of the craniofacial complex, which has been largely adapted from Ten Cate's *Oral Histology Textbook* (Nanci 2007). We also briefly review well-established molecular concepts at play in craniofacial patterning and some of the more recent developments in this field. In this context, processes have been abridged and only detailed when necessary for logical flow. For a more comprehensive treatise, readers are referred to this chapter's references.

The cranial region of early jawless vertebrates comprised (1) cartilaginous elements to protect the notochord and the nasal, optic, and otic sense organs (neurocranium); and (2) cartilaginous rods supporting the branchial (pharyngeal) arches in the oropharyngeal region (viscerocranium). Together, the neurocranium and the viscerocranium formed the chondrocranium. As vertebrates evolved, they came to develop jaws through modification of the first arch cartilage, with the upper portion becoming the maxilla and the lower portion the mandible. In addition, they acquired larger sensory elements resulting in a significant expansion of the head region. Bony skeletal elements (the dermal bones), evolved for protection, formed the vault of the skull and the facial skeleton that included bony jaws and teeth. The cephalic expansion required a new source of connective tissue that was achieved by the epitheliomesenchymal transformation of cells from the neuroectoderm. Indeed, the neural origin of craniofacial bones distinguishes them from other skeletal bones, and may, in part, explain why in certain cases bones at these two sites are differentially affected (e.g., osteoporosis). Comparison between the cranial components of the primitive vertebrate skull and the cranial skeleton of a human fetus is shown in Figure 1.1.

## Head formation

Neural crest cells (NCCs) from the midbrain and the first two rhombomeres transform and migrate as two streams to provide additional embryonic connective tissue needed for craniofacial development (Figure 1.2). The first stream provides much of the ectomesenchyme associated with the face, while the second stream is targeted to the first arch where they contribute to formation of the jaws. NCCs from rhombomere 3 and beyond migrate into the arches that will give rise to pharyngeal structures. Since homeobox (Hox) genes are not expressed anterior to rhombomere 3, a different set of coded patterning genes has been adapted for the development of cephalic structures. This new set of genes, reflecting the later development of the head in evolutionary terms, includes the Msx (muscle segment Hox), Dlx (distal-less Hox), Barx (BarH-like Hox) gene families.

## Branchial arches and formation of the mouth

The mesoderm in the pharyngeal wall proliferates, forming as six cylindrical thickenings known as *branchial* or *pharyngeal arches*. Four of these arches are major; the fifth and sixth arches are transient structures in humans. The arches expand from the lateral wall of the pharynx toward the midline.

The inner aspect of the branchial arches is covered by endoderm (with the exception of the ectoderm of the

*Mineralized Tissues in Oral and Craniofacial Science: Biological Principles and Clinical Correlates*, First Edition.
Edited by Laurie K. McCauley, Martha J. Somerman.

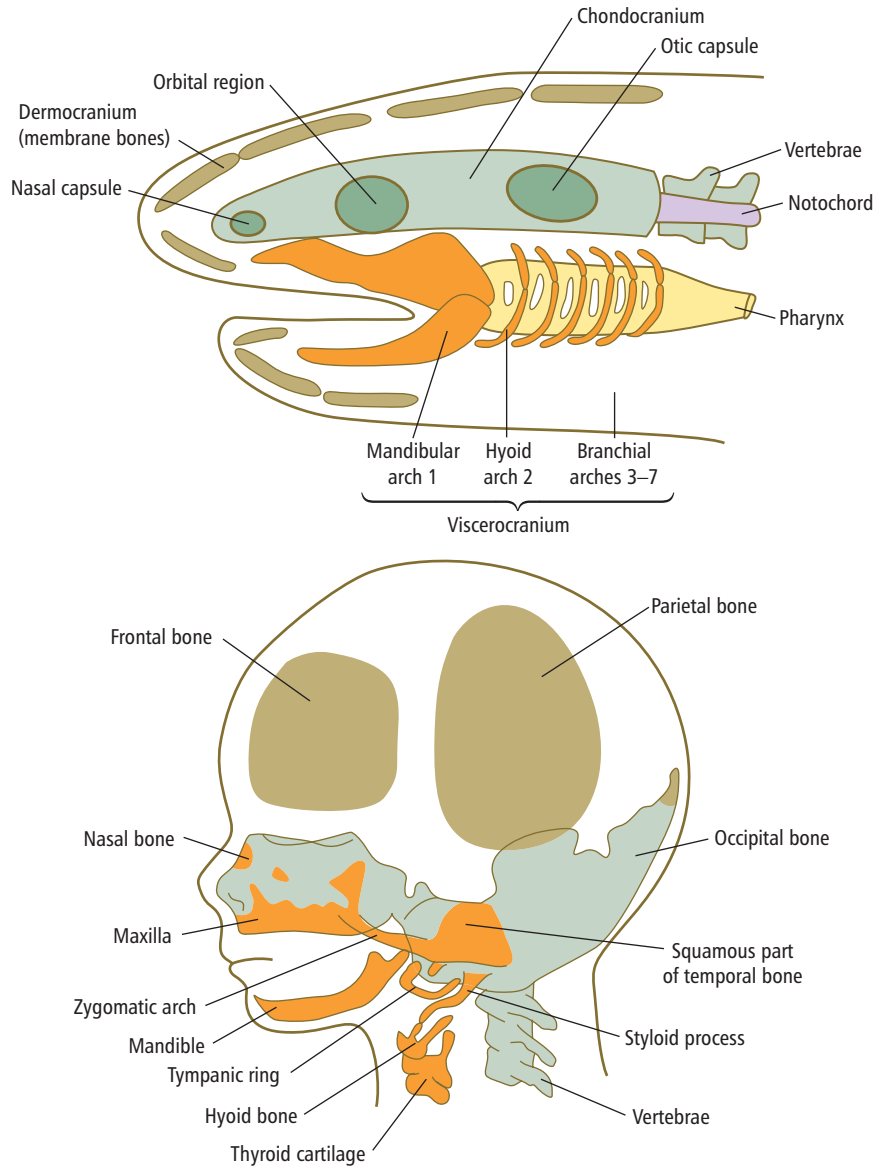


**Figure 1.1** The major components of the primitive vertebrate cranial skeleton and the distribution of these same components in a human fetal head. (Adapted from Carlson 2004, with permission from Elsevier Ltd.)

first arch because it forms in front of the buccopharyngeal membrane). The central core consists of mesenchyme derived from lateral plate mesoderm that is invaded by NCCs. The resulting ectomesenchyme condenses to form a bar of cartilage, the arch cartilage. The cartilage of the first arch is called *Meckel's cartilage*, and that of the second is *Reichert's cartilage*; the remaining arch cartilages are not named.

The primitive oral cavity is at first bounded above (rostrally) by the frontal prominence, below (caudally) by the developing heart, and laterally by the first branchial arch. With the midventral expansion of arches, the cardiac plate is pushed away, and the floor of the mouth is formed by the first, second, and third branchial arches. At about the middle of the fourth week of gestation, the first branchial arch establishes the maxillary process, so that the oral cavity is limited cranially by the frontal prominence covering the rapidly expanding forebrain, laterally by the newly formed maxillary process, and ventrally by the first arch (now called the *mandibular process*; Figure 1.3).

## Formation of the face, primary palate, and odontogenic epithelium

Early development of the face is dominated by the proliferation and migration of ectomesenchyme involved in the formation of the primitive nasal cavities. At about 28

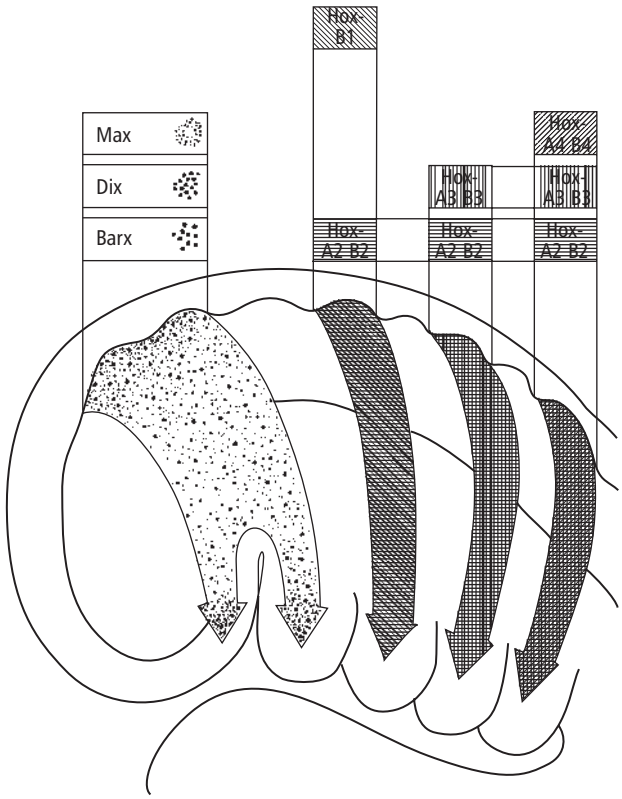


**Figure 1.2** Migrating neural crest cells (NCCs) express the same homeobox (Hox) genes as their precursors in the rhombomeres from which they derive. Note that Hox genes are not expressed anterior to rhombomere 3. A new set of patterning genes (Msx, Dlx, and Barx) has evolved to bring about the development of cephalic structures so that a "Hox code" also is transferred to the branchial arches and developing face. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

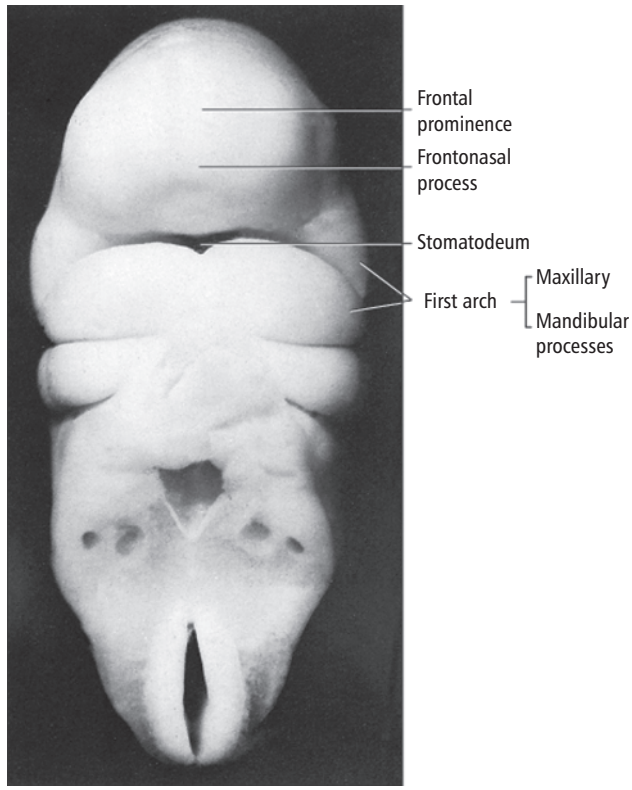


**Figure 1.3** A 27-day embryo viewed from the front. The beginning elements for facial development and the boundaries of the stomatodeum are apparent. The first arch gives rise to maxillary and mandibular processes. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

days, two localized thickenings develop within the ectoderm of the frontal prominence just rostral to the oral cavity. The mesenchyme at the periphery of these so-called olfactory placodes undergoes rapid proliferation giving rise to two horseshoe-shaped ridges on the frontal prominence. The lateral arm of the horseshoe is called the *lateral nasal process*, and the medial arm is called the *medial nasal process*. The region of the frontal prominence, where these changes take place and the nose will develop, is now referred to as the *frontonasal process*.

The maxillary process grows medially and approaches the lateral and medial nasal processes (Figure 1.4). The medial growth of the maxillary process pushes the medial nasal process toward the midline, where it merges with its anatomic counterpart from the opposite side. The medial nasal processes of both sides, together with the frontonasal process, give rise to the middle portion of the nose, the middle portion of the upper lip, the anterior portion of the maxilla, and the primary palate. The maxillary process fuses with the lateral nasal process to form the lateral wings of the nose and cheek areas.

The face develops between the 24th and 38th days of gestation. As fusion of facial processes occurs, the epithelium on the inferior border of the maxillary and medial nasal processes and the superior border of the mandibular arch begin to proliferate and thicken. These thickened areas will soon give rise to an arch-shaped continuous plate of odontogenic epithelium on both the maxilla and the mandible.

## Formation of the secondary palate

Initially, there is a common oronasal cavity bounded anteriorly by the primary palate. The subsequent development of the secondary palate creates a distinction between the oral and nasal cavities. Its formation commences between seven and eight weeks and completes around the third month of gestation. Three outgrowths appear in the oral cavity: the nasal septum grows downward from the frontonasal process along the midline, and two palatine shelves, one from each side, extend from the maxillary processes toward the midline. The

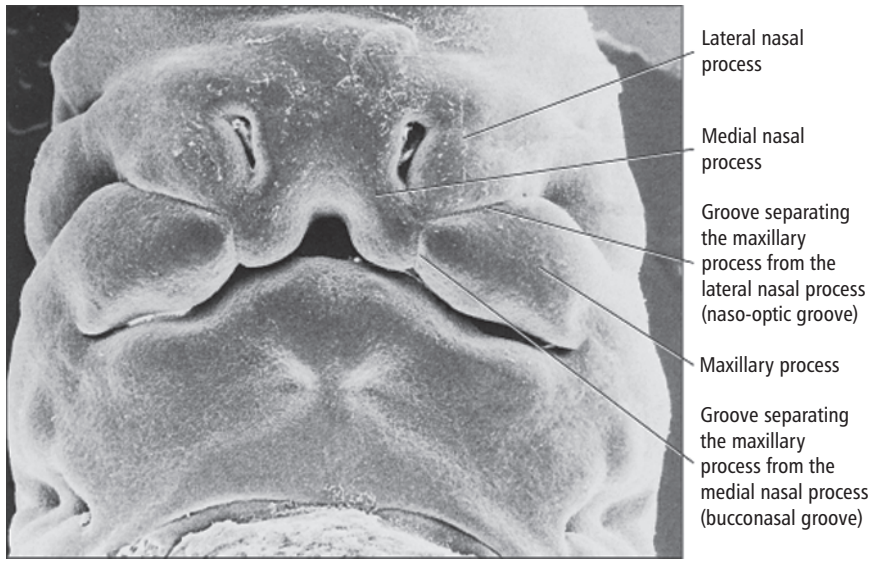


**Figure 1.4** Scanning electron micrograph (SEM) of a human embryo at around six weeks. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

septum and the two shelves converge and fuse along the midline, thus separating the primitive oral cavity into nasal and oral cavities. As the two palatine shelves meet, adhesion of the epithelia occurs. The epithelial cells at the seam undergo epitheliomesenchymal transformation, and they acquire mesenchymal characteristics and the ability to migrate, thus establishing continuity between the fused processes. The closure of the secondary palate proceeds gradually from the primary palate in a posterior direction.

## Development of the skull

The skull can be divided into three components: the cranial vault, the cranial base, and the face (Figure 1.5). Membranous bone forms the cranial vault and face while the cranial base undergoes endochondral ossification. Some of the membrane-formed bones may develop secondary cartilages to provide rapid growth.

Intramembranous bone formation was first recognized when early anatomists observed that the fontanelles of fetal and newborn skulls were filled with a connective tissue membrane that was gradually replaced by bone during the development and growth of the skull. During this process, ectomesenchymal cells proliferate and condense at multiple sites within each bone of the cranial vault, maxilla, and body of the mandible. At these sites of condensed mesenchyme, osteoblasts differentiate and begin to produce bone. This first embryonic bone forms rapidly and is termed *woven bone*. At first, the woven bone takes the form of spicules and trabecules, but progressively these forms fuse into thin bony plates

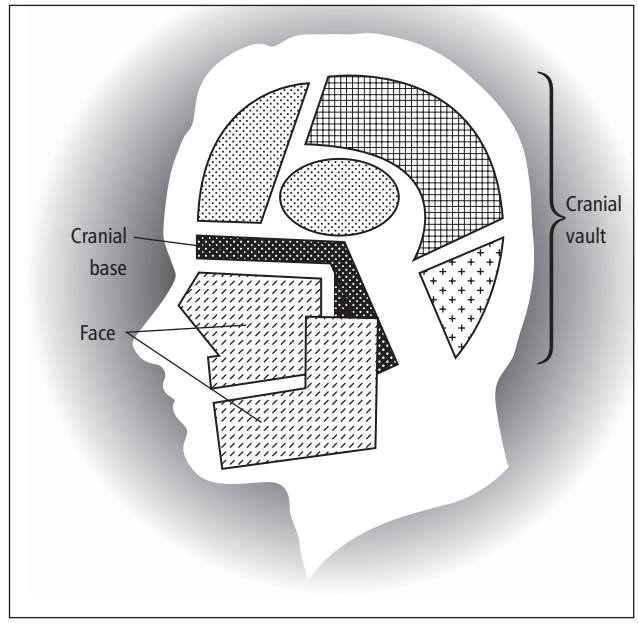


**Figure 1.5** Subdivisions of the skull. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

that may combine to form a single bone. In general, there is resorption on endosteal surfaces and bone formation on periosteal ones. However, depending on adjacent soft tissues and their growth, segments of the periosteal surface of an individual bone may contain focal sites of bone resorption. For instance, growth of the tongue, brain, and nasal cavity and lengthening of the mandible body require focal resorption along the periosteal surface.

Conversely, segments of the endosteum of the same bone simultaneously may become a forming surface, resulting in bone drift. Woven bone of the early embryo and fetus turns over rapidly. There is a rapid transition from woven bone to lamellar bone during late fetal development and the first years of life.

As fetal bones begin to assume their adult shape, continued proliferation of soft connective tissue between adjoining bones brings about the formation of sutures and fontanelles. Sutures play an important role in the growing face and skull. Found exclusively in the skull, sutures are the fibrous joints between bones. However, sutures allow only limited movement. Their function is to permit the skull and face to accommodate growing organs such as the eyes and brain.

The periosteum of a bone consists of two layers: an outer fibrous layer and an inner cellular or osteogenic layer apposed to the surface of the bone. At sutures, the outer fibrous layers of the two adjacent bones involved in the joint extend and fuse across the gap between the bones. The osteogenic layer and part of the fibrous layer of each bone run down through the gap between the bones. When these are forced apart, for example by the growing brain, the structural arrangement at the suture allows bone formation at the margins while keeping the bones separated yet strongly tied together.

Endochondral bone formation occurs at the articular extremity of the mandible and base of the skull. Early in embryonic development, a condensation of ectomesenchymal cells occurs. Cartilage cells differentiate from these cells, and a perichondrium forms around the periphery, giving rise to a cartilage model that eventually is replaced by bone.

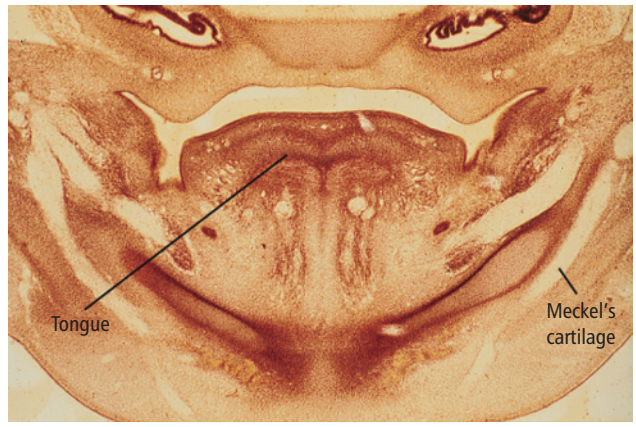


**Figure 1.6** Slightly oblique coronal section of an embryo demonstrating almost the entire extent of Meckel's cartilage. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

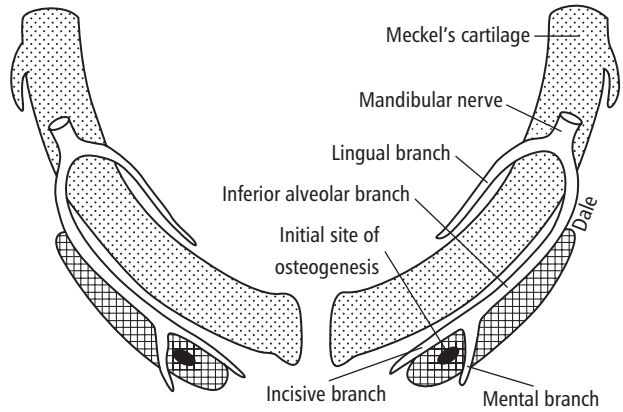


**Figure 1.7** Site of initial osteogenesis related to mandible formation. Bone formation extends from this anteriorly and posteriorly along Meckel's cartilage. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

## Development of the mandible and maxilla

As indicated above, the mandible and the maxilla form from the tissues of the first branchial arch, the mandible forming within the mandibular process and the maxilla within the maxillary process that outgrows from it.

### *Mandible*

The cartilage of the first arch (Meckel's cartilage) forms the lower jaw in primitive vertebrates. In human beings, Meckel's cartilage has a close positional relationship to the developing mandible but is believed to make no direct contribution to it. At six weeks of development, this cartilage extends as a solid hyaline cartilaginous rod surrounded by a fibrocellular capsule from the developing ear region (otic capsule) to the midline of the fused mandibular processes (Figure 1.6). The two cartilages of each side do not meet at the midline but are separated by a thin band of mesenchyme.

On the lateral aspect of Meckel's cartilage, during the sixth week of embryonic development, a condensation of ectomesenchyme occurs in the angle formed by the division of the inferior alveolar nerve and its incisor and mental branches. At seven weeks, intramembranous ossification begins in this condensation, forming the first bone of the mandible (Figure 1.7). From this center of ossification, bone formation spreads rapidly anteriorly to the midline and posteriorly toward the point where the mandibular nerve divides into its lingual and inferior alveolar branches. This spread of new bone formation occurs anteriorly along the lateral aspect of Meckel's cartilage, forming a trough that consists of lateral and medial plates that unite beneath the incisor nerve. This trough of bone extends to the midline, where it comes into approximation with a similar trough formed in

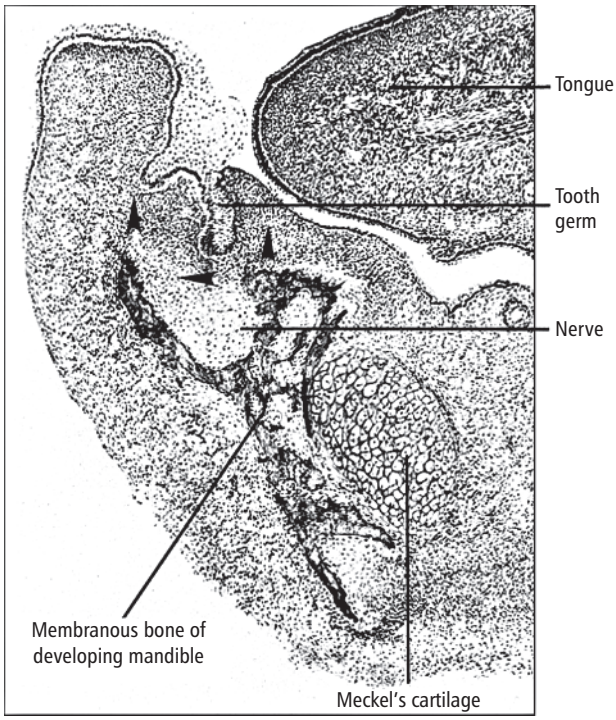


**Figure 1.8** Photomicrograph of a coronal section through an embryo showing the general pattern of intramembranous bone deposition associated with formation of the mandible. The relationship among nerve, cartilage, and tooth germ is evident. Arrowheads indicate the future directions of bone growth to form the neural canal and lateral and medial alveolar plates. (Reprinted from Nanci 2007, with permission from Elsevier Ltd.)

the adjoining mandibular process (Figure 1.8). The two separate centers of ossification remain separated at the mandibular symphysis until shortly after birth.

Similarly, a backward extension of ossification along the lateral aspect of Meckel's cartilage forms a gutter that is later converted into a canal that contains the inferior alveolar nerve. This backward extension of ossification proceeds in the condensed mesenchyme to the point where the mandibular nerve divides into the inferior alveolar and lingual nerves. From this bony canal, medial and lateral alveolar plates of bone develop in relation to the forming tooth germs so that the tooth germs occupy a secondary trough of bone. This trough is partitioned, and thus the teeth come to occupy individual compartments that are finally enclosed totally by growth of bone over the tooth germ (Figure 1.8). The ramus of the mandible develops by a rapid spread of ossification posteriorly into the mesenchyme of the first arch, turning away from Meckel's cartilage. Thus, by 10 weeks the rudimentary mandible is formed almost entirely by membranous ossification, with no apparent involvement of Meckel's cartilage.

The further growth of the mandible until birth is influenced strongly by the appearance of three secondary cartilages and the development of muscular attachments: (1) the condylar cartilage, which is most important; (2) the coronoid cartilage; and (3) the symphyseal cartilage.

The condylar cartilage appears during the 12th week of development and rapidly forms a cone-shaped or carrot-shaped mass that occupies most of the developing ramus. This mass of cartilage is converted quickly to bone by endochondral ossification so that at 20 weeks, only a thin layer of cartilage remains in the condylar head. This remnant of cartilage persists until the end of the second decade of life, providing a mechanism for growth of the mandible in the same way as the epiphyseal cartilage does in the limbs.

The coronoid cartilage appears at about four months of development, surmounting the anterior border and top of the coronoid process. Coronoid cartilage is a transient growth cartilage and disappears long before birth. The symphyseal cartilages, two in number, appear in the connective tissue between the two ends of Meckel's cartilage but are entirely independent of it. They are obliterated within the first year after birth.

### *Maxilla*

The maxilla also develops from a center of ossification in the mesenchyme of the maxillary process of the first arch. No arch cartilage or primary cartilage exists in the maxillary process, but the center of ossification is associated closely with the cartilage of the nasal capsule. As in the mandible, the center of ossification appears in the angle between the divisions of a nerve (i.e., where the anterosuperior dental nerve is given off from the inferior orbital nerve). From this center, bone formation spreads posteriorly below the orbit toward the developing zygoma and anteriorly toward the future incisor region. Ossification also spreads superiorly to form the frontal process and downward to form the lateral alveolar plate for the maxillary tooth germs. Ossification also spreads into the palatine process to form the hard palate. The medial alveolar plate develops from the junction of the palatine process and the main body of the forming maxilla. This plate, together with its lateral counterpart, forms a trough of bone around the maxillary tooth germs that eventually become enclosed in bony crypts.

A secondary cartilage also contributes to the development of the maxilla. A zygomatic, or malar, cartilage appears in the developing zygomatic process and for a short time adds considerably to the development of the maxilla. At birth, the frontal process of the maxilla is well marked, but the body of the bone consists of little more than the alveolar process containing the tooth germs and

small though distinguishable zygomatic and palatine processes. The body of the maxilla is relatively small because the maxillary sinus has not developed. This sinus forms during the 16th week as a shallow groove on the nasal aspect of the developing maxilla.

## Molecular aspects of craniofacial development: concepts and recent developments

NCC subpopulations, depending on their anteroposterior location within the neural tube, are subject to a very complex set of signaling events. A plethora of molecules is being used as cues to guide them to their ultimate destination within a restricted area of the head. The ventrolateral segmentation and migration of NCCs toward branchial arches and their eventual differentiation are tightly controlled through reciprocal signaling by neighboring cells from the endoderm and ectoderm. All molecules involved are controlled both temporally and spatially. The contribution of many of them has been deciphered with the use of genetically altered animal models (mouse, zebra fish, and chick) that often recapitulate human syndromes caused by mutations in corresponding genes.

The anteroposterior fate of NCCs is believed to be acquired before migration, but some plasticity may occur depending on environmental cues. The Hox family of transcription factors is instrumental in specifying the branchial arch. Since in evolutionary terms the head developed later, Hox genes are not expressed rostral to the first branchial arch, and the development of cephalic structures relies on a new set of coded Hox patterning genes that includes the transcription factors Otx2 (orthodenticle Hox 2), Msx, Dlx, Barx, and probably others that have not yet been fully characterized. In the second branchial arch, Hoxa2 functions to modulate the competence of NCCs toward skeletogenic signaling by fibroblast growth factors (FGFs), resulting in negative regulation of several downstream transcriptional regulators such as Pitx1 (paired-like homeodomain transcription factor 1), Lhx6 (LIM Hox protein 6), Six2 (sine oculis Hox 2), Alx4 (aristaless-like Hox 4), Bapx1 (bagpipe Hox or nk3 Hox 2), and Barx1 (BarH-like Hox 1) that are normally expressed in the first branchial arch. The mechanisms leading to the activation and repression of Hox genes in the cranial region and hindbrain are also very complex in nature, depending on epigenetic regulations and FGF8 signaling. These mechanisms provide another level of complexity, indirectly affecting transcriptional events. Notably, the remodeling machinery that modifies chromatin architecture renders DNA more or less accessible to transcription factors and co-factors. Modifier enzymes that target nucleosomal histones (i.e., acetyltransferase and demethylase) have been described that have profound effects on craniofacial patterning.

Environmental factors that transmit repulsive and/or attractive signals are also instrumental in specifying the segregation and fate of NCCs in their migration to branchial arches. Several secreted ligands and their membrane-bound receptors provide repulsive cues, especially in the NCC-free regions of mesenchyme adjacent to rhombomeres 3 and 5. Among others, important players in this process are the membrane-anchored receptors Erbb4 (v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4), ephrin, and neurolipin, along with their respective soluble ligands, neuregulins, ephrins, and semaphorins. On the other hand, directional guidance (attraction) of NCCs into their respective arches is provided by another elaborate set of species-specific molecules, such as Twist, Tbx1 (T-box 1), Sdf1b/Cxcr4a (stromal cell–derived factor 1/chemokine cxc motif receptor 4), Npn1/Vegf (neuropilin 1/vascular endothelial growth factor), and Fgfr1 (fibroblast growth factor receptor 1). Intracellular-signaling cascade events and crosstalk eventually culminate in eliciting various cellular responses including proliferation, migration, differentiation, and survival or apoptosis.

Interestingly, even though both mandibular and maxillary primordia originate from similar NCCs and possess similar molecular features, they develop into very different structural entities. In the first branchial arch, a gradient of gene expression involving the Dlx family of transcription factors (1–6), the so-called intra-arch Dlx code, promotes coordinated gene expression along the dorsoventral axis that regulates jaw patterning. Distinct sets of Dlx family members are important for determining the identity of the mandible (Dlx1/2/5/6) versus the maxilla (Dlx1/2). A dramatic demonstration of the importance of the selective set of Dlx molecules in jaw specification is observed in mice lacking both Dlx5 and Dlx6 genes. Lack of Dlx5/6 causes a reversal of the mandible into a maxilla, generating an animal with two mirror-image upper jaws. Dlx5/6 activate expression of other downstream transcription factors—Dlx3/4, Hand1/2 (heart- and neural crest derivatives–expressed 1 and 2), Alx3/4, Pitx1, Gbx2 (gastrulation brain homeobox 2), and Bmp7 (bone morphogenic protein 7)—important for mandibular development processes, and repress others, such as Pou3f3 (pou domain class 3, transcription factor 3), Foxl2 (forkhead box l2), and Irx5 (Iroquois Hox protein 5), that are themselves important for maxillary processes and under the control of Dlx1/2. Thus, Dlx family members are critical for determining the identity of the mandible versus the maxilla. Another level of complexity is brought about by

local environmental signaling crosstalk that directly or indirectly modulates the transcriptional Dlx program. One such regulator is endothelin, a secreted molecule produced mostly by the ectoderm that signals through the endothelin receptor Ednra in NCCs and promotes, possibly through Mef2C (mads box transcription enhancer factor 2 polypeptide c), Dlx5/6 expression. Targeted ablation of the endothelin pathway in mice causes duplication of maxillary processes, whereas ectopic expression induces duplication of mandibular processes. Other signaling events, coming from the endoderm, such as Vegf and Shh (sonic hedgehog), or the ectoderm—Fgf, Bmp, and Wnt (wingless-type mouse mammary tumor virus [MMTV] integration site family)—also promote dorsoventral guidance by modulating many different processes, such as migration, survival, apoptosis, and/or differentiation.

More recently, posttranscriptional mechanisms contributing to the regulation of NCC development have been uncovered. Of mention is the effect of specific micro-RNAs (miRNAs) that control the half-life of targeted gene messenger RNAs (mRNAs) by interacting with the 3′ untranslated region and thus repressing translation and/or targeting for degradation. For instance, the expression of miR-452, abundant in early NCCs, directly targets Wnt5A, consequently lowering the activity of downstream effector signaling molecules Shh and Fgf8, at least in the mandibular region of the first branchial arch. miR-452 is an indirect positive modulator of Dlx2 expression, itself controlled by Fgf8. Another function attributed to Wnt5a is the activation of noncanonical Wnt pathways through the Frizzled (Fzd) and activating Disheveled (Dsh) proteins that regulate the orientation of cell structures through the planar cell polarity (Pcp) genes. The effects of Pcp, promoting cell-to-cell contacts, are to induce a coordinated polarized migratory path of NCCs in the branchial arch, and to induce cartilage outgrowth and chondrogenesis of cranial base structures and the nasal septum.

The species-specific patterning of the head and face, especially the shape and size of the beak and muzzle, has been suggested to depend on the canonical (beta-catenin-dependent) Wnt signaling pathway that seems to be an upstream modulator of critical effector molecules, such as Fgf8, Bmp2, and Shh, present in the frontonasal ectodermal zone (FEZ) center. FEZ is another major determinant of species-specific patterning and outgrowth of the upper face. Variation in the organization, relative size, and position of the FEZ, together with other molecules like calcium-dependent calmodulin, is partly responsible for the very different shapes encountered in nature. These data indicate the complexity of the various pathways that contribute to facial outgrowth by regulating cell proliferation and differentiation.

## Conclusions, futures orientations, and clinical perspectives

In this chapter, we have described the basic embryological events and provided an overview of major signaling interactions and molecules implicated in craniofacial development and morphogenesis. While our understanding of molecular analyses has made significant progress, the cell biological activities resulting from various molecular cascades remain largely unexplored. Planar polarity genes are attracting much attention not only because of their role in regulating cell polarity and morphogenesis, but also because of their implication in positioning cellular structures and coordinating activities such as cell intercalation. One such structure is the cilium that is found on the surface of most vertebrate cells and acts as a mechanical and chemical sensor. Ciliary dysfunction is present in some syndromes, such as facial-digital syndrome and Bardet–Biedl syndrome that exhibit facial changes, as well as cleft palate and micrognatia. Experimentally, it has been shown that a neural crest–targeted mutation of the kif3 gene, encoding for a kinesin-like protein implicated in cilogenesis and intraflagellar transport, affects polarized growth and cell shape, resulting in shortened mandibles and defects in development of the cranial base. It is worth noting that some phenotypes resulting from ciliopathies are linked to perturbations of signaling pathways, including that of Wnt.

Current treatments for craniofacial malformations such as craniosynostosis (premature fusion of sutures) and cleft lip and palate are essentially surgical. Such interventions can in some cases lead to serious complications or require multiple interventions. Clearly, a better understanding and especially integration of cell, tissue, and molecular events implicated in craniofacial development and formation are necessary for the rational design of genetic and pharmacological strategies for correcting malformations. While interventions after birth with novel therapeutic approaches would represent a major improvement, the eventual ability to intervene in utero would allow correcting problems early on so that subsequent development could follow its normal course. In utero interventions to correct aberrant signaling could exploit recent developments in gene therapy and the stem and progenitor potential of NCCs. The feasibility of successful prenatal manipulations, however, still remains in the realm of wishes for now because of the extremely early (first weeks of gestation) and narrow

window in which potential intervention would need to be performed.

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