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Embryology and skull growth: what is important for the neurosurgeon?

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Abstract The present chapter proposes a quick journey in craniofacial development and growth during embryology. The pivotal stages and mechanisms are presented with a developmental and evolutionary (evo-devo) perspective. The origin and role of the cranial neural crest cells (a vertebrate innovation) are used as a red thread to decipher the pivotal interactions between epithelia and mesenchyme and corresponding signaling pathways in craniofacial morphogenesis. Together with the different modes of ossification of the different skull units either mesoderm- or neural crest-derived, this chapter attempts to illustrate the integrative nature of the head and skull. The physical interactions and molecular signaling centers active during craniofacial development are illustrated by the relations between the growing brain and skull, as well as the interactions between the chondrocranium and dermatocranium. I hope this chapter will be of interest for the neurosurgeons by providing perspectives that might not be common in more traditional literature dealing with growth anatomy and embryology of the skull.

Keywords: development, evolution, neural crest, mesoderm, dermatocranium, chondrocranium, animal models

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Embryology and skull growth: what is important for the neurosurgeon? 1

Foreword

As a biological anthropologist, I was trained in Anatomy and Evolution. During my postdoc in the Richtsmeier lab in the Department of Anthropology at the Pennsylvania State University I had the opportunity to study developmental biology and birth defects such as craniosynostosis which then became central to my research. The purpose of this chapter is to present the embryology and growth of the skull from an evolutionary and developmental perspective (evo-devo). As such, the goal of this chapter is not to provide an up to date highly detailed description of skull embryology and early skull growth in humans. Those data have been previously published by other authors and should be consulted for a thorough treatment of these important topics. Many helpful reviews and original research exist in the current literature. For my chapter, I have leaned heavily on “Larsen’s human embryology” by Gary Schoenwolk et al. [1], “Craniofacial embryogenetics and development” by Geoffrey H. Sperber and Steven M. Sperber [2], and “Bones and cartilage” by Brian K. Hall [3].

From fertilization to gastrula: fundamental processes

Though the initial two days of human embryo formation is under the control of factors expressed only by the oocyte, subsequent differentiation of cells is governed by the genetic material inherited from both parents. Three days after the fertilization of the ovum by the spermatozoon that results in the formation of the totipotential zygote, the first mitotic cycles have produced 16 smaller pluripotential cells achieving the morula stage. In addition to the expression of genetic material within the cell, interactions between cells and their environment are essential for differentiation. These interactions between newly differentiated cells happen by induction. Induction can occur by direct cellular contact, diffused agents, or agents embedded in vesicles targeting mechanisms such as gene activation or inactivation, protein translation, modification of cell membrane selectivities, intercellular adhesion or repulsion, and cell migration. Timing is an additional dimension which is crucial to normal development. Alteration or disruption of this complex symphony referred to as morphogenesis can lead to abnormal development.

With the end of the first week after fertilization (preimplantation period), the embryonic period starts with the implantation of the blastocyst (around 100 cells at the time) into the decidual layer of the uterine wall. The embryonic period comprises seven weeks of embryogenesis. The polarized blastocyst consists of an outer layer (trophoblast) and an inner cell mass adherent to the trophoblast, filling only one part of the newly formed blastocyst cavity. Eventually, the inner cell blast will give rise to the definitive structures of the fetus, while the trophoblast will form the extra-embryonic tissues.

At day 10, newly formed structures called fetal membranes are visible: the chorion deriving from the trophoblast and delimiting the embryo; the amnion, a membrane delimiting the future amniotic sac filled with amniotic fluid; the yolk sac, providing nutrition and gas exchange before the forming placenta becomes functional; and the allantois, a transient sac allowing gas exchange and liquid waste handling. With the establishment of the two layers, the dorso-ventral axis is defined. The 2-layer germ disk is connected dorsally to the amnion through the epiblast and ventrally to the yolk sac through the hypoblast. The germ disk, amnion, and yolk sac derive from the inner cell blast.

Between day 14 and 17, a process called gastrulation initiates and will reorganize the two-layer blastocyst into a three-layer embryo (gastrula) consisting of ectoderm, mesoderm, and endoderm. Signaling pathways such as Hedgehog (HH), fibroblast growth factor (FGF), wingless (Wnt), bone morphogenetic protein (BMP), and Notch are active and regulate the activity of Nodal (a transforming growth factor beta, TGF- β) that is essential to the formation of mesoderm and the establishment of left-right asymmetry of visceral organs. At the caudal end of the 2-layer germ disk, Nodal signaling causes epiblast cells to proliferate, differentiate, and migrate toward the midline of the germ disk. This accumulation of cells produces a bulge and ultimately forms a linear band of cells called the primitive streak. The primitive streak elongates cranially in the midline and the progression stops when the streak is about halfway across the embryonic disk. While the lengthening stops, epiblast cells are still migrating toward the rostral end of the primitive streak creating the primitive node, and thereby establishing the cranial-caudal axis. The primitive node is a major signaling center and will subsequently induce the formation of the neural plate and notochord rostrally (see below). Epiblast cells continue to migrate towards the primitive streak and primitive node and eventually pass through the primitive groove and primitive pit, respectively, via a process known as ingression. Ingression is made possible by the epithelial-mesenchymal transition (EMT, see for a review [4]) in which epiblast cells lose their polarity and adhesive properties and migrate ventrally to form a layer between the epiblast and hypoblast. Through EMT, these cells proliferate and form the intraembryonic mesoderm. As the ingression process continues, the hypoblast and epiblast form the endoderm and ectoderm, respectively. The embryonic disk is now trilaminar and the three primary germ layers, ectoderm, endoderm, and mesoderm, will give rise to all structures and organs of the body.

The role of the primitive node is essential during gastrulation. At day 16, epiblast cells migrating through the primitive node differentiate to form the notochord which develops cranially and stops caudally to the prechordal plate. The notochord, surrounded ventrally by the endoderm, dorsally by the ectoderm, and laterally by the mesoderm (now called paraxial mesoderm), is achieved around day 20.

Neurulation: A focus on cranial neural crest cells

One of the main evolutionary innovations of the vertebrates is the appearance of an embryonic stem-cell population from the neuroectoderm called the neural crest. With the “new head hypothesis”, Gans and Northcutt [5] proposed that many elements of the vertebrate head represent an addition rather than a modified portion of the protochordates’ trunk. More precisely, anterior structures such as sensory, integrative, and motor systems, as well as the associate supportive skeletal structures derive from the neural crest and epidermal placodes [5]. These structures are pivotal in functions such as detection and capture of prey as well as exchange and distribution of respiratory gases [5].

The specification of neural tissues creates the neural plate which is an ectodermal structure that forms cranially to the primitive node and dorsally to the forming notochord (i.e. notochordal process). The neural plate results from a process called neural induction when signaling (down regulation of *BMP* by *FGF*) causes the apicobasal thickening of epiblast cells. The neural plate then elongates cranially along the midline. The neural plate is composed of neural ectoderm and is separated from the nonneural ectoderm by the neural plate border that will give rise to a population of stem cells called the neural crest and to placodes during the process of neurulation. Neurulation, the transformation of the neural plate into neural tube, is induced and regulated by *TGF-beta* signaling molecules such as Chordin and Noggin that down-regulate BMP signaling [6], as well as FGFs [7], Wnt signals [8] and a Dlx gradient [9]. At day 19, a neural groove appears in the neural ectoderm. The neural groove is bordered laterally by the neural folds is formed through ingression of the neural plate. The folding process and the fusion of the neural folds allow the formation and closure (dorsally) of the neural tube at day 21. The neural crest cells also undergo ingression through EMT and pass momentarily between the ectoderm (dorsally) and the neural tube (ventrally) [10] as they begin their migration process. The closure of the cranial and caudal openings of the neural tube (neuropores) takes place on day 24 and 26-28, respectively.

The neural crest cells are multi-potent stem cells unique to vertebrates that arise on the dorsal aspect of the embryo and stretch from the cranial to the caudal tip. Neural crest cells migrate, proliferate, and differentiate into various tissues (connective, muscle, nervous, endocrine) and pigment cells (melanocytes). Martik’s et al. [11] work on lamprey (jawless fish; agnatha) led them to propose that the neural crest of early vertebrates formed a single and uniform cell population similar to neural crest cells of the amniote trunk, and that during early vertebrate evolution a new subpopulation of neural crest cells appeared; the cranial neural crest. These authors propose that Hox genes and other regulatory modifications are sufficient to account for the small transcriptional differences observed between the cranial and trunk neural crest subpopulations. Co-option of distinct genes into a cranial neural crest-specific module likely allowed the cranial neural crest gene regulatory network to progressively give rise to morphological novelties such as the lower jaw [11]. After induction, cranial neural crest cells migrate to the frontonasal process and the first four pharyngeal arches [12–14]. Throughout interactions with neighboring structures such as surface ectoderm, neuroectoderm and endoderm, neural

crest cells contribute to the development of many cranial structures and are critical to normal development of the craniofacial region [15]. Cranial neural crest give rise to the frontal bone, most bones of the facial skeleton, and most facial connective tissues.

The dorsal closure of the neural tube (day 21) ends the presomite period and initiates the somite period marked by the appearance of 42-44 bilaterally paired blocks of paraxial mesoderm along the rostro-caudal axis of the embryo that are characteristic of segmented animals: the somites. Intermediate and lateral plate mesoderm are situated lateral to the paraxial mesoderm. Somitogenesis starts rostrally with paraxial mesoderm condensations forming incompletely segmented structures called somitomeres. Cranial somitomeric mesoderm migrates ventrally to contribute to the future pharyngeal arches. Caudal to the somitomeres, a craniocaudal sequence characterizes the formation of the somites establishing the segmented nature of the body with 4 occipital, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 8-10 coccygeal somites. The segmentation of the somites is driven by a number of 'clock' genes. Periodical activation of these clock 'genes' generates a signaling wave propagating in the rostral direction involving *Notch*, *Wnt* and *FGF*. Boundaries between somites are formed through EMT. The somites subsequently differentiate into three parts: the sclerotome (ventromedial aspect), dermatome (lateral aspect), and myotome (intermediate portion). The sclerotome contributes to the vertebral column except in the occipital region where it fuses to form the occipital bone. The dermatome gives rise to the dermis of the skin. The myotome differentiates into muscles. By the end of the somite period the cardiovascular, digestive, respiratory, nervous, urinary, and reproductive systems are established. The optic and otic placodes, which will give rise to the eyes and internal ears, respectively, are formed. It is also the time when the embryo folds ventrally. At day 31, the head of the embryo is composed of a prominent brain ventrally associated with the pharyngeal arches prefiguring the face and neck, altogether flexed over the developing heart due to this folding. At this time the nasal placode and limb buds are also visible. The post somite period initiates at day 32. Head development occurs at the center of the post somite period when eyes, ears, and nose acquire a human characteristic morphology. At the end of the post somite period (day 56, end of the eighth week), the embryo is termed a fetus.

Role of neural crest cells in head development: the example of the frontonasal ectodermal zone (FEZ)

At the end of the fourth week (day 28), while the neural tube is closed, the cranial most section of the embryo experiences major expansion, bending, folding, and constriction. The neural tube then forms three primitive brain regions: the prosencephalon or forebrain, the mesencephalon or midbrain, and the rhombencephalon or hindbrain. The segmentation process goes on and at the end of the seventh week

(day 49), the secondary brain regions are visible. The prosencephalon gives rise to the telencephalon and diencephalon, and the rhombencephalon to the metencephalon and myelencephalon. Later on, the telencephalon will differentiate into the cerebral cortex, hippocampus, basal ganglia, basal forebrain nuclei, and olfactory bulbs. The diencephalon will differentiate into the thalamus and hypothalamus and neural portion of the eye. The metencephalon will differentiate into the cerebellum and pons, and the myelencephalon into the medulla (for a review on brain patterning and associated signaling pathways see [16]).

During the fourth week of development (at the time the neural tube is closing) seven prominences prefiguring the face and organized around the stomodeum (future mouth) are visible: the midline frontonasal prominence and three paired lateral structures, the lateral nasal (sometimes considered part of the frontonasal prominence), maxillary and mandibular prominences. The maxillary and mandibular prominences derive from the first pharyngeal arch. Craniofacial development results from interactions between neural crest cells and the surrounding epithelia such as the neural ectoderm of the forebrain, the facial ectoderm of the frontonasal prominence and pharyngeal arches, as well as the endoderm of the inner surface of the pharyngeal arches. Pioneering experiments on chick and quail by Le Douarin and lab members showed that the fate of neural crest cells is restricted by *Hox* genes such as *Hoxa2* (reviewed in [17]). However, the neural crest is not pivotal in the formation and patterning of the pharyngeal arches. The pharyngeal endoderm is involved in the patterning of the pharyngeal arch skeleton [18].

Many transcription factors contribute to craniofacial development. Brugman et al. (2008), for example, provide a review that highlights the role of FGF8 in normal craniofacial development. Fgf8 signaling from the neuroectoderm promotes development of the jaws in birds, while expression of *Fgf8* in the first branchial arch ectoderm is dependent on signaling from the neural crest [19]. This illustrates how interactions between epithelia and mesenchyme are pivotal to craniofacial morphogenesis. Another key signaling pathway in craniofacial development is associated to *sonic hedgehog* (*Shh*) from the Hedgehog family. *Shh* expression takes place in the prosencephalon, then in the ventral part of the telencephalon [20]. Shh signaling is pivotal for proper morphogenesis of the frontonasal prominence. Fgf and Shh signaling emanating from the forebrain neuroectoderm are essential for the patterning and differentiation of the frontonasal neural crest [21]. Of particular importance to facial development is the frontonasal ectodermal zone (FEZ). The FEZ was defined by Hu et al. [22] as a key signaling center for the morphogenesis of the face located in the surface cephalic ectoderm in mammals and avians. The FEZ is formed by the boundary between *Shh* and *Fgf8* expressing cells located within the frontonasal prominence ectoderm [22]. While the FEZ is a single site of expression, in mice the FEZ is divided into paired regions associated with the median nasal prominence [23]. *Shh* expression in the FEZ starts with the arrival of NC cells into the frontonasal prominence and is probably induced and maintained by Bmps [24]. Several ectopic transplantation experiments demonstrated that the FEZ induces skeletogenesis, determine the dorsoventral polarity of the upper jaw as well as its

morphogenesis through patterning of the underlying mesenchymal cells [22, 23]. However, when the FEZ was transplanted into regions expressing Homeobox genes such as the second pharyngeal arch, no effects on the mesenchymal cells was observed [23]. FEZ positively regulates *Bmp* expression in NC mesenchyme of the upper jaw in birds [23] and as such participates in craniofacial phenotypic variation. For example, Young et al [25] showed that down-regulation of *Shh* in the brain caused a continuous narrowing of the frontonasal prominence, hypotelorism, and medial maxillary rotation, while up-regulation of *Shh* causes the opposite phenotype. Besides physical interactions between the developing brain and face (e.g. see [26] on the role of brain growth on the positioning of the facial prominences and eyes), FEZ is an example of molecular signaling center active in craniofacial morphogenesis.

The different units of the skull in evolutionary and developmental biology

The skull is a complex skeletal system whose primary function is to protect the brain and the major sense organs (olfactory, optic, and auditory) as they carry out their functions. Multiple and sometimes conflicting definitions of the different elements of the skull exist depending on authors' area of study; e.g., human anatomy, comparative anatomy, embryology, evolution, or developmental biology. The skull is often compartmentalized into divisions on the basis of varying criteria and/or based on certain developmental derivatives. Examples of these divisions include regions or modules labeled as: facial skeleton, braincase, cranial base, cranial vault, chondrocranium, splanchnocranium, dermatocranium, pharyngeal skeleton, and viscerocranium. Most researchers and clinicians have a fairly clear idea of what each division comprises, though these definitions are rarely made explicit. To more clearly define aspects of the craniofacial skeleton, Kawasaki and Richtsmeier [27] proposed to follow nomenclature used in evolutionary and developmental biology that defines the skull into the cranial endoskeleton (composed of the chondrocranium and pharyngeal skeleton) and the cranial dermal skeleton (dermatocranium). The pharyngeal skeleton, composed primarily of cartilage, arose as simple gill supports in stem jawless vertebrates and became specialized into the more complex lower jaw that includes the ear ossicles. The chondrocranium, composed of cartilage and cartilage bone arose to support the brain. The dermatocranium composed primarily of dermal bone, enamel and enameloid was the last to evolve [28]. Bone forming from the endoskeletal precursors (cartilage bone) and from the dermal or exoskeleton (dermal bone and membrane bone) are distinct ontogenetically and/or phylogenetically [29, 3]. Dermal bone of the exoskeleton forms in contact with the epithelial ectoderm through intramembranous ossification, whereas the endoskeleton forms mainly through endochondral ossification but not in contact with the epithelial ectoderm.

The two principal skeletal tissues are bone and cartilage (the other two being enamel and dentin). Cranial cartilage and bone that forms endochondrally and intramembranously can derive from either the mesoderm or neural crest. Endochondral ossification is a process in which cartilaginous models are replaced by bone. Intramembranous ossification occurs when aggregated mesenchymal cells directly differentiate into osteoblasts and form bone. In both types of ossification, bone consists of cells distributed on a collagen matrix that is mineralized into a vascularized skeletal tissue. Ossification per se starts with the condensation of mesenchymal cells and up-regulation of tissue-specific genes. Condensation consists of successive stages; initiation, formation of boundaries, cell adhesion, proliferation, growth and end of growth [3].

Osteoblasts manufacture the extra cellular matrix called osteoid and also mineralize that matrix trapping themselves within the mineralized tissue where they differentiate into osteocytes and function in bone homeostasis. Bone grows by apposition and mineralization of new osteoid perichondrially (outer surface of cartilage), periosteally (outer surface of bone), or endosteally (inner surface of bone).

Cartilage consists of cells and extra cellular matrix that may or may not mineralize and is avascular. Cartilage is formed by chondroblasts and chondrocytes and resorbed by chondroclasts. The extracellular matrix is rich in water, glycosaminoglycans, and type II collagen. Cartilage grows by apposition, but unlike bone it can also grow interstitially and is therefore capable of changing its shape rather quickly during development.

Though the two modes of ossification are active in craniofacial development, the relationship between the chondrocranium and dermatocranium during intrauterine development remains elusive. This is in part related to the transient nature of the chondrocranium. However, a recent study by Motch et al. [30] provide experimental data on mouse model for Crouzon syndrome (*Fgfr2c*^{C342Y/+}) supporting the existence of a developmental relationship between cartilaginous elements of the chondrocranium and bones of the dermatocranium. Together with the data published earlier by Kawasaki and Richtsmeier [27] and Pitirri et al. [28], these studies lead the members of this group to hypothesize that the chondrocranium is pivotal in establishing the initial formation and spatial distribution of the dermal bones during embryogenesis. These authors propose that the chondrocranial elements serve as a scaffold guiding and influencing the location and morphology of developing dermal bones. If these results were to be confirmed in future studies, they would advocate for a reassessment of the classic definition of intramembranous ossification which is not supposed to involve cartilage elements.

Neural crest vs. mesoderm-derived tissues and premature suture fusion

Bones forming the craniofacial skeleton are either derived from cranial neural crest or paraxial mesoderm. The facial skeleton, anterior parts of the braincase floor, the squamous temporal, and frontal bones are derived from the cranial neural crest. The mesoderm gives rise to the occipital bones, parietal bones and the non-squamous part of the temporal bone [31–33]. Many of these bones articulate at cranial sutures (and synchondroses) which form major bone growth sites as long as the mesenchyme forming the suture remains undifferentiated [34]. As a consequence, the coronal suture forms a boundary between neural crest and mesoderm derived bones of the skull.

When a craniosynostosis-associated mutation is present in a human patient, that mutation is present in all cells of the body – including all bone cells whether derived from neural crest or from mesoderm. Laboratory animals and recent developments in Cre-mediated DNA recombination provides an established method for conditional control of gene expression in animal models. There exist Cre-LoxP systems that allow spatial and/or temporal control over recombination of the target gene. For example, it is possible to create an Apert mouse model bearing a Cre-inducible mutation on fibroblast growth factor receptor 2 (*Fgfr2*^{S252W}). When using mesoderm-specific Cre driver (i.e. *Mesp1Cre*) and neural crest-specific Cre driver (i.e. *Wnt1Cre*) and such Cre-inducible Apert mouse model, it then becomes possible to express the Apert mutation only in mesoderm- or neural crest-derived tissues [35].

Premature fusion of the coronal suture (i.e. coronal craniosynostosis) can be caused by the expression of the *Fgfr2*^{S252W} Apert syndrome mutation in the mesoderm derived mesenchyme of the coronal suture in mouse. In conditional expression mouse model for Apert syndrome, the expression of this mutation is responsible for abnormal osteogenesis though it does not alter the lineage border integrity between mesoderm and neural crest [35]. Subsequent study on the same mouse models showed that the conditional expression of the *Fgfr2*^{S252W} mutation in suture mesenchyme of other craniofacial sutures was not sufficient to induce its premature fusion and that suture-specific variation in the timing of fusion might also play a significant role [36]. Though mice expressing the *Fgfr2*^{S252W} mutation only in the neural crest-derived tissues possess a patent coronal suture at birth, these mice displayed a more severe phenotype than the mice expressing this same mutation only in the mesoderm-derived tissues (and possessing a fused coronal suture) [36]. This can be explained by the fact that the majority of the craniofacial bones are neural crest-derived and that mice expressing the *Fgfr2*^{S252W} mutation only in the neural crest-derived tissues displayed premature fusion of several facial sutures such as the premaxillary-maxillary, maxillary-palatine, and maxillary-zygomatic sutures.

Paralleling the dual nature of brain influence on craniofacial development (physical and molecular), beside the primary effect on craniofacial phenotype of the expression of a specific mutation, secondary effects related to physical interactions

between the neural-crest derived and mesoderm-derived tissues exist as well. Indeed, both mouse models conditionally expressing the FGFR2 S252W mutation either in the neural crest- or mesoderm-derived tissues also displayed dysmorphologies in bones not expressing the mutation. The authors proposed that these secondary changes could be caused by four potential sources : (1) disrupted morphogenesis of the bone not expressing the mutation caused by a neighboring prematurely fused suture; (2) displacement of the bone not expressing the mutation caused by neighboring dysmorphic mutant bones; (3) abnormal physical constraints of soft tissues expressing the mutation; and (4) abnormal signaling or soluble factors produced by mutant cells that alter the development of the neighboring non-mutant cells [36].

Conclusion: what is important for the neurosurgeon?

This chapter is an attempt to deliver a solid, not-too-detailed summary of early development of the whole embryo and then of bones of the head which, I hope, will be of interest for the neurosurgeons. Throughout this chapter, the complex developmental stages and associated mechanisms were described with an evolutionary and developmental perspective. After the first three weeks of development and the establishment of the three primary germ layers, I focused on the activities of cranial neural crest cells during neurulation with some insights on their evolutionary origin. A focus was then provided with the interesting example of the frontonasal ectodermal zone illustrating the pivotal role of interactions between epithelia and mesenchyme in craniofacial morphogenesis. The FEZ also allowed to illustrate the integrative nature of craniofacial development with the complex interactions between the growing brain and skull either through physical interactions or molecular signaling centers. Subsequently, osteogenesis of the skull was described providing evolutionary and developmental perspective on the cranial endoskeleton formed by the chondrocranium and pharyngeal skeleton, and the cranial dermal skeleton or dermatocranium. The work from the Richtsmeier group was used to illustrate how the chondrocranial elements might serve as a scaffold guiding and influencing the location and morphology of developing dermal bones. Finally, through the example of conditional expression of *Fgfr2*^{S252W} Apert syndrome mutation in mouse models, the role of sutures in craniofacial morphogenesis was described as well as the nature of the interactions between the mesoderm- and neural crest-derived craniofacial bones.

Surgical techniques to operate patients with craniosynostosis, either syndromic or non-syndromic, sometimes focus on the rearrangement of bones that make up the facial skeleton and cranial vault. However, we need to remember that these causative mutations (for a review see [37]) affect all cells and all tissues (soft and hard) and that understanding how different tissues impact the growth pattern of other is critical to proper correction of craniofacial anomalies.

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