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FORMATION OF NEURAL CREST AND ORGANOGENESIS IN MAMMALS:A REVIEW

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Abstract: Neural crest cells are actually multi-potential stem cells that contribute extensively to vertebrate development and give rise to different cell and tissue types. Determination of the fate of mammalian neural crest has been inhibited by the lack of markers. Here, we make use of a two-component genetic system for indelibly marking the offspring's of the cranial neural crest during tooth and mandible formation. This paper briefly describes the formation of different parts from neural crest.[1]

Keywords: Otic vesicle (OV), Endolymphatic duct (ED), Semicircular canals (SCC), Cochleovestibular ganglion (CVG), Nonspecific cytotoxic cells(NCC), Stria vascularis (SV), Sympathoadrenal lineage (SA), Cranial neural crest (CNC)

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INTRODUCTION

Neural crest cells are a transient, multipotent, migratory cell population unique to vertebrates that gives rise to a diverse cell lineage including melanocytes, craniofacial cartilage and bone, smooth muscle, peripheral and enteric neurons and glia.[2]

It develops from ectoderm as shown in figure1. "One hundred years ago, claiming that an ectodermal derivative such as the neural crest was in any way involved with the formation of skeletal structures was the embryological and evolutionary equivalent of nailing an additional thesis to the cathedral door," wrote Langille and Hall in the early 1990s, referring to Martin Luther's famous Protestant rebellion. "That skeletal structures were mesodermal in origin was dogma, known and accepted by all; an ectodermal origin was heresy."[3]

Some cells from the neural folds give rise to pleuripotent neural crest cells that migrate widely in the embryo and give rise to many nervous structures:

1. Formation of ear
2. Formation of mouth
3. Formation of tooth
4. Formation of sensory nerves
5. Spinal ganglia (dorsal root ganglia)
6. Ganglia of the autonomic nervous system
7. Ganglia of some cranial nerves
8. Sheaths of peripheral nerves
9. Meanings of brain and spinal cord
10. Formation of adrenal medulla
11. Skeletal and muscular components in the head[4]

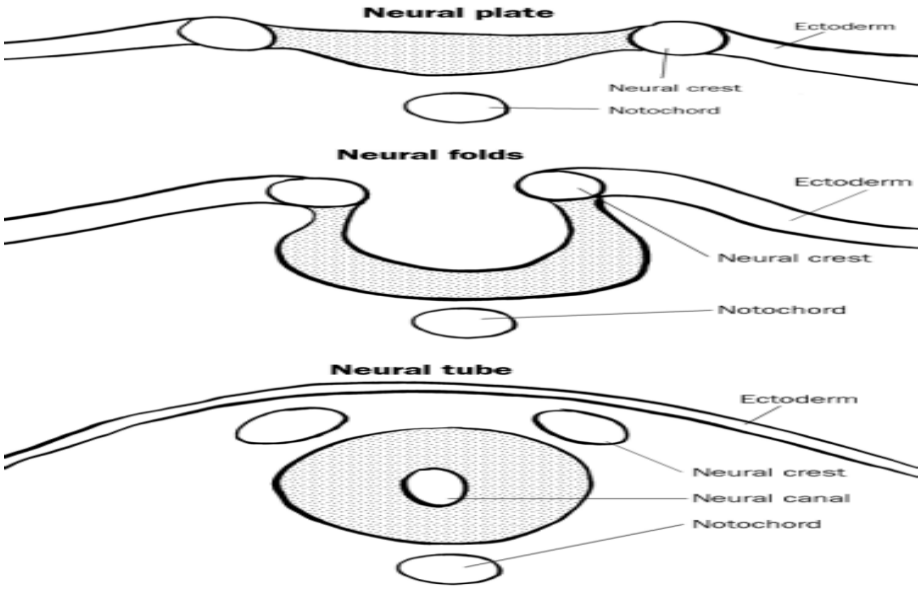

Fig. 1: Formation of Neural Crest in Mammals

Formation of Ear in Mammals from Neural Crest:

Cranial sensory placodes are thickenings of ectoderm that are the source of complex sensory organs and ganglia that innervate the head and neck. The otic placode is induced next to the hindbrain and invaginates into the head to form the otic cup. The otic cup then closes off from the surface ectoderm of the head, thus creating the OV. Neuroblasts are specified within the otic epithelium and delaminate into the mesenchyme where they condense to form the CVG.[5]

The OV undergoes morphogenesis to give rise to the inner ear labyrinth, a continuous epithelium that makes up the vestibular [endolymphatic duct (ED), semicircular canals (SCC), utricle, saccule and auditory (cochlea) components of the inner ear . This is accompanied by development of six sensory patches: three cristae (at the base of each SCC), two maculae (utricular, saccular) and the organ of Corti(within the cochlea). Sensory epithelia are defined by the presence of mechanosensory hair cells that are associated with supporting cells and innervated by CVG neurons. To date, it is widely accepted that the otic placode ectoderm is the only source for the inner ear labyrinth and neurons of the CVG.[6]

Contributions of other tissues to inner ear development include melanocytes, which are derived from NCCs. NCCs are specified in the dorsal neural tube and migrate throughout the embryo. Cranial NCC migratory streams are organized by rhombomeric segments of the hindbrain and respond to cues from the pharyngeal endoderm .In mice, melanocyte progenitor cells originate from the mid brain hind brain junction and cervical trunk regions of the neural tube, and then migrate around the inner ear later in development to give rise to the

intermediate cells of the stria vascularis (SV) that is located along the lateral wall of the cochlea.[7]

Formation of Mouth and Tooth in Mammals from Neural Crest:

The cranial neural crest cells, which are specialized cells of neural origin, are central to the process of mammalian tooth development. They are the only source of mesenchyme able to sustain tooth development, and give rise not only to most of the dental tissues, but also to the periodontium, the surrounding tissues that hold teeth in position. Tooth organogenesis is regulated by a series of interactions between cranial neural crest cells and the oral epithelium. In the development of a tooth, the epithelium covering the inside of the developing oral cavity provides the first instructive signals. Signaling molecules secreted by the oral epithelium.

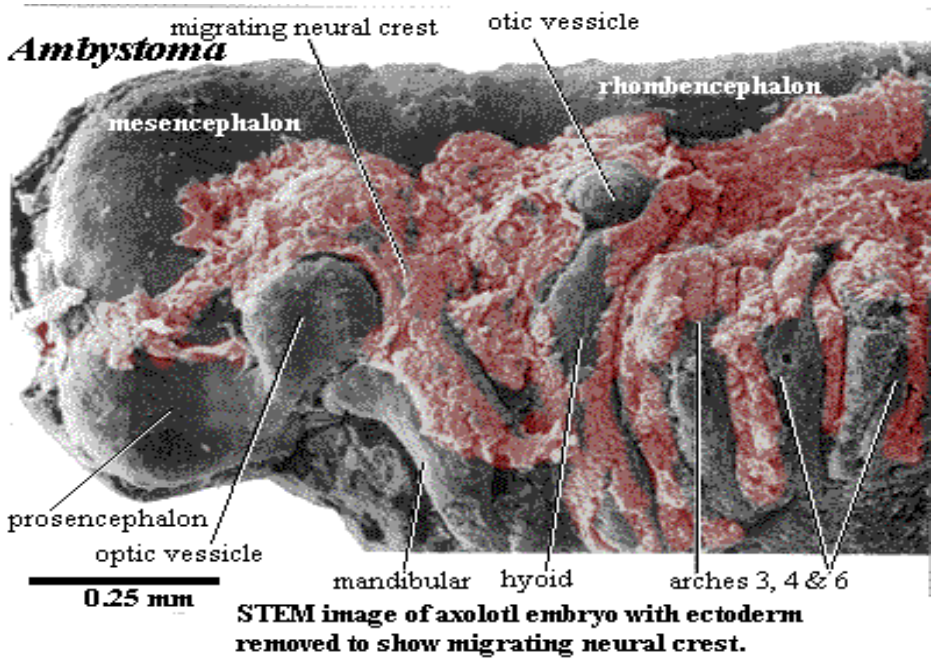

Fig. 2: Formation of Mouth and Tooth in Mammals from Neural Crest

1) Establish large cellular fields competent to form a specific tooth shape (mono- or multicuspid) along a proximodistal axis.

2) Define an oral (capable of forming teeth) and non-oral mesenchyme along a rostrocaudal axis.

3) Position the sites of future tooth development. The critical information to model tooth shape resides later in the neural crest-derived mesenchyme. Cranial neural crest cells ultimately differentiate into highly specialized cell types to produce mature dental organs. Some cranial

neural crest cells located in the dental pulp, however, maintain plasticity in their developmental potential up to postnatal life, offering new prospects for regeneration of dental tissues.[8]

Formation of Ganglia of the Autonomic Nervous System, some Cranial Nerves , Sheaths of Peripheral Nerves and Sensory Nerves:

In mammals, the peripheral nervous system is derived from two distinct embryonic cell populations, the neural crest and ectodermal placodes. Neural crest cells arise from the hinges of the invaginating neural plate, while ectodermal placodes form in pairs from discrete, usually thickened, head ectoderm lateral to the neural tube. While these two populations generally contribute to different structures in the nervous system, the exception is where they converge to form the cranial sensory ganglia of the trigeminal (V), facial (VII), glossopharyngeal (IX), and vagal (X) cranial nerves. The dual embryonic origin of cranial sensory ganglia has intrigued investigators for some time, but surprisingly little is known about the neural crest–placode relationship. The process of cranial gangliogenesis exemplifies a fascinating problem on how cell–cell interactions drive assembly of complex structures in the developing embryo.[9]

The somatosensory system mediates fundamental physiological functions, including the senses of touch, pain and proprioception. This variety of functions is matched by a diverse array of mechanosensory neurons that respond to force in a specific fashion. Mechanotransduction begins at the sensory nerve endings, which rapidly transform mechanical forces into electrical signals and develops from the neural crest. Progress has been made in establishing the functional properties of mechanoreceptors, but it has been remarkably difficult to characterize mechanotranducer channels at the molecular level. However, in the past few years, new functional assays have provided insights into the basic properties and molecular identity of mechanotransducer channels in mammalian sensory neurons. The recent identification of novel families of proteins as mechanosensing molecules will undoubtedly accelerate our understanding of mechanotransduction mechanisms in mammalian somatosensation.[10]

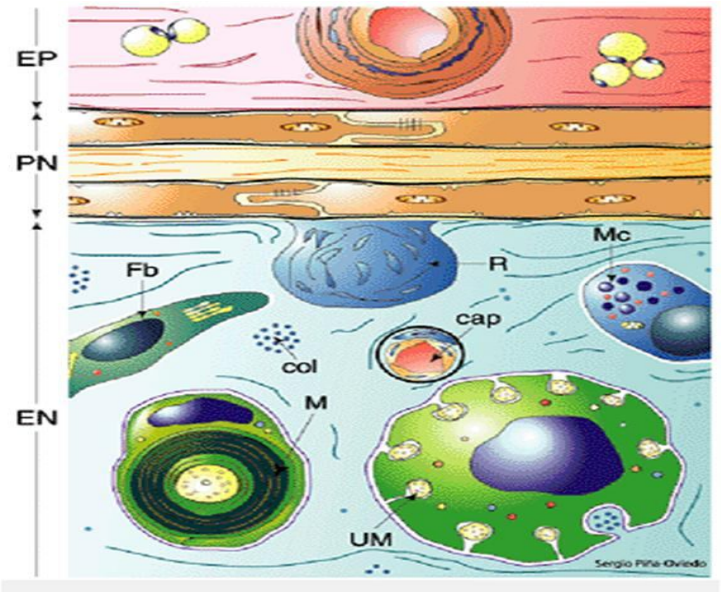

Fig. 3:Formation of Peripheral Nervous System & Autonomic Ganglia

Formation of Adrenal Medulla:

Chromaffin cells in the adrenal medulla are neuroendocrine cells derived from neural crest. Together with the sympathetic neurons of the dorsal ganglia and the intermediate small intensely fluorescent cells, they constitute the sympathoadrenal lineage (SA) of neural crest derivates . All these cells derive from common SA progenitor cells that migrate during early embryogenesis and acquire along their migratory route the specific characteristics of mature catecholamine producing cells . However, unlike sympathetic neurons, the cells from adrenal medulla are able to proliferate throughout life. [11]

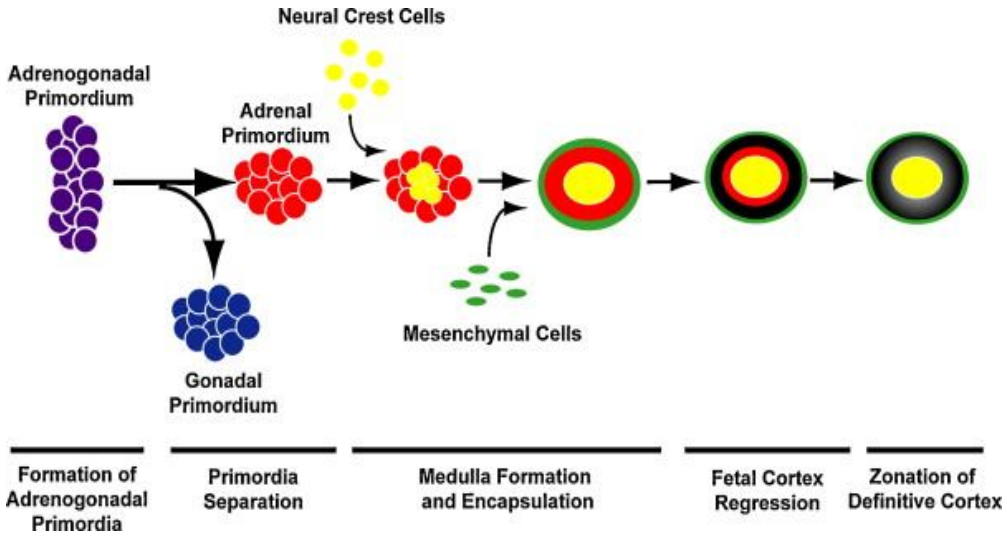

Fig. 4:Formation of Adrenal Medulla

Formation of Cardiac Neural Crest in Mammals:

The neural crest is a migratory population of cells that originate from the dorsal aspect of the neural tube. Neural crest cells form at all axial levels of the embryo, and assume a variety of ectodermal and mesodermal fates as they reach peripheral. A variety of experimental approaches indicate that a specific crest cell population, termed the cardiac neural crest, is responsible for morphogenesis of the out flow region of the developing heart.[12]

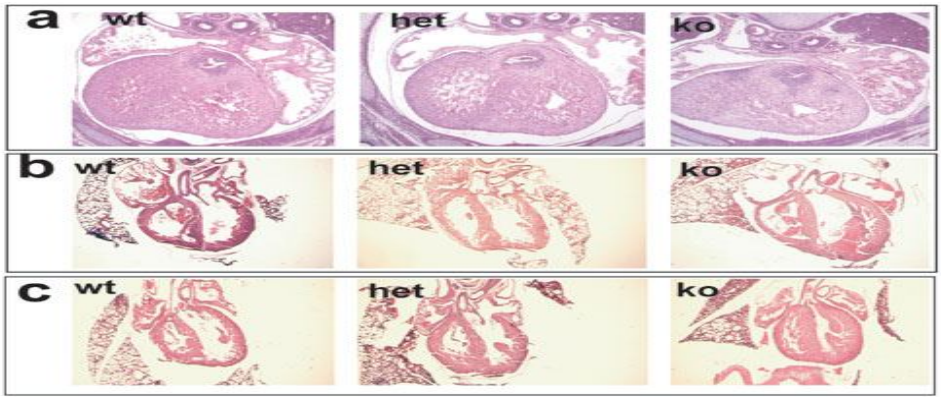

Fig. 5:Formation of Cardiac Neural Crest in Mammals

Injection of lineage tracers into mammalian embryos ex utero or cultured in vitro has demonstrated that neural crest cells populate the pharyngeal arches in a manner similar to avian embryos, but these do not provide sufficient cell labeling or allow embryonic survival to demonstrate the behavior of crest cells in the morphogenesis of the outflow region of the heart. A number of molecular markers, both endogenous and transgenic have been useful in marking the initial population of migratory cardiac neural crest, but most suffer from either being no longer expressed at stages after occupancy of the pharyngeal arches, or from ectopic sites of expression such that expression does not necessarily correlate with a neural crest cell origin. A transgenic line in which β-galactosidase is expressed from the connexin 43 promoter has to date been the most reliable marker of mammalian cardiac neural crest cell fate but expression of this transgene is extinguished in mid to late gestation. Furthermore, all of these molecular markers are potentially subject to altered expression patterns after genetic or teratogenic manipulation, making their use in defining crest cell fate in an experimental context less reliable.[13-14]

Formation of Skeletal and Muscular Components in the Head in Mammals:

The skeleton of the skull, face and jaws develops from precursor tissues derived from two embryonic sources: the cranial neural crest (CNC) and the cranial paraxial mesoderm. In birds and mammals, the viscerocranium (skeleton of the jaw and face) is formed predominantly by skeletogenic cells derived from the CNC while the neurocranium (the vault and the base of the skull), contains both CNC and mesoderm derivatives. [15]

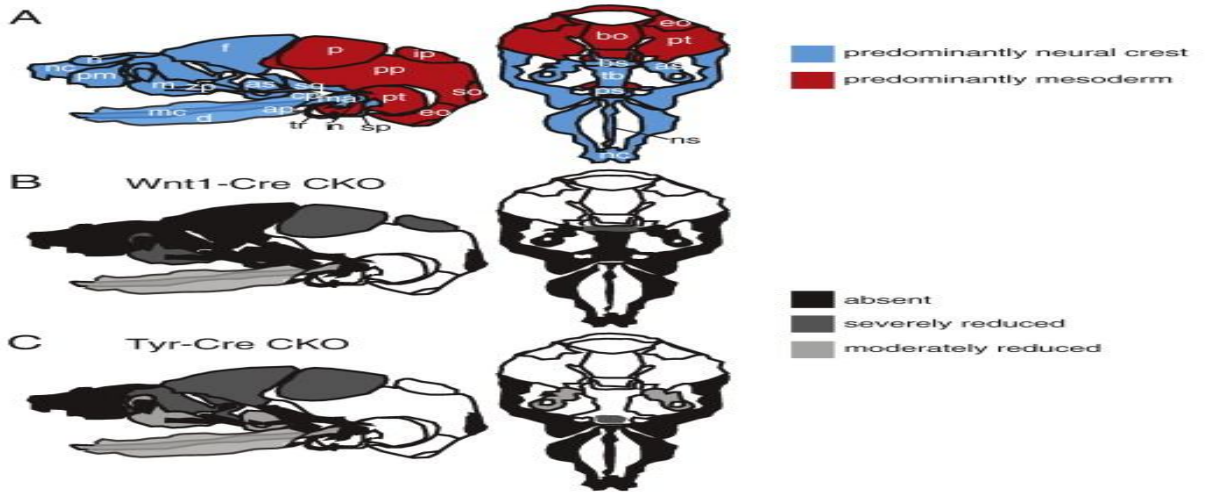

Fig. 6:Formation of Skeletal and Muscular Components in the Head in Mammals

Explanation with Examples in Different Mammals:

Neural Crest Formation and Organogensis in Mouse and Human Embryos:

The fate of the mammalian cardiac neural crest is only poorly defined. In mouse and human embryos, a number of genetic and teratogenic manipulations result in defects such as persistent truncus arteriosus, aortic arch artery abnormalities, and/or thymic, thyroid or parathyroid deficiencies. The spectrum of these malformations so closely resembles those seen in neural-crestablated avian embryos that it has long been inferred that there is a mammalian equivalent to the avian cardiac neural crest and that these manipulations interfere with some aspect of mammalian cardiac neural crest biology. However, it has not been possible in mammalian embryos to label neural crest cells, either by transplantation or injection, in a manner that allows long-term survival of the recipient embryo.16

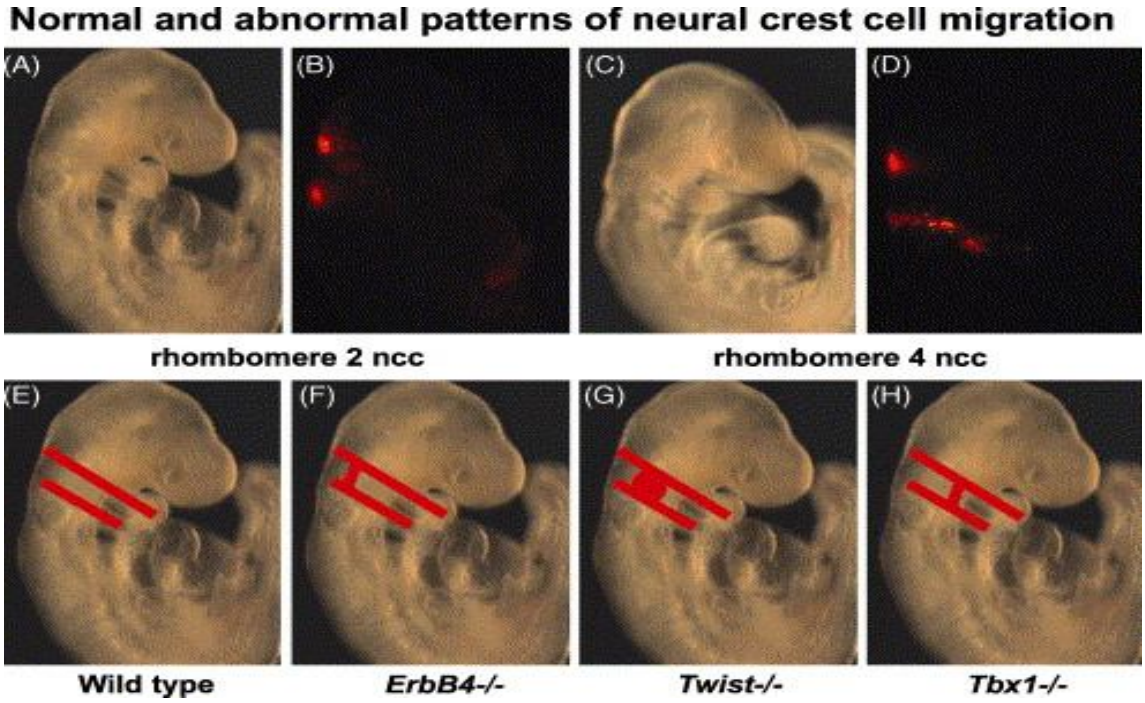

Fig. 7:Neural Crest Formation & Organogenesis in Mouse

In mouse embryos, Twist1, which encodes a basic helix–loop–helix (bHLH) transcription factor, is expressed in the paraxial mesoderm surrounding the neural tube of the early-somite embryo. Later, Twist1 is expressed in the CNC-derived mesenchyme of the frontonasal region and in the branchial arches, which contain both CNC- and mesoderm-derived cells. Twist1 is down-regulated in the branchial arch mesoderm by E9.5. Loss of Twist1 leads to major malformations of the craniofacial structures, suggesting that Twist1 is required for the differentiation of CNC and mesoderm-derived tissues. Twist1-null mutant embryos also display closure defects of the cephalic neural tube , despite the absence of Twist1 expression in the neural tube. In chimaeras with a low (< 25%) contribution of Twist1-null embryonic stem cells in the cranial mesenchyme, the brain and neural tube develop normally even when Twist1-deficient cells are present in the neuro epithelium. This finding suggests that Twist1 function is required specifically in the cranial mesenchyme for normal brain morphogenesis.

Absence of Twist1 function impacts on the development of the CNC and the formation of CNC-derived tissues. Twist1-deficient CNC cells transplanted to the upper hindbrain of wild-type host embryos can initiate migration and home in to the first branchial arch. However, they fail to colonize the sub-ectodermal zone of the arch that is normally populated by the CNC cells. Instead, they are sequestered in the core of the arch where mesodermal cells are normally localized .Twist1-deficient cells are similarly localized to the core of the branchial arch in chimeras generated from mutant ES cells and wild-type host embryos .[17]

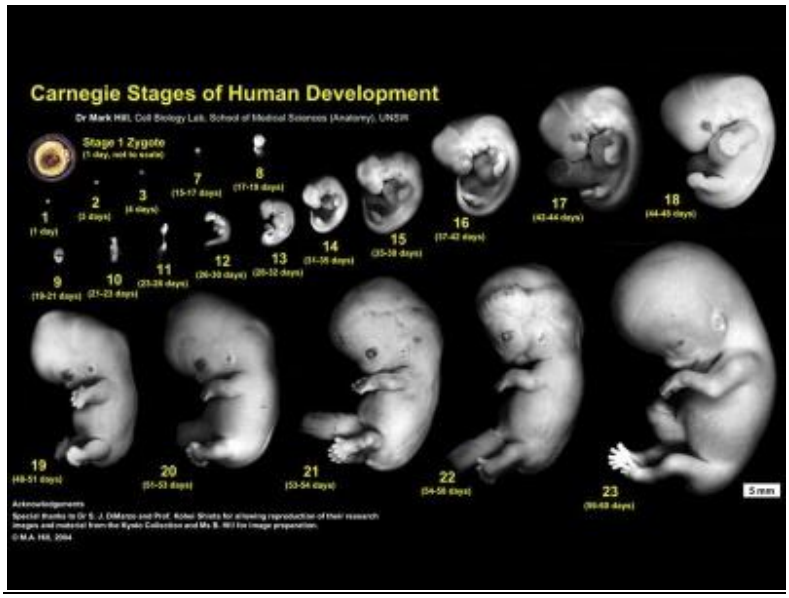

Fig. 8:Neural Crest Formation & Organogenesis Human Embryos

Conclusion:

The mammalian dentition is composed of serial groups of teeth, each with a distinctive crown and root morphology, highly adapted to its particular masticatory function. In the embryo, generation of individual teeth within the jaws relies upon interactions between ectoderm of the first branchial arch and the neural crest-derived ectomesenchymal cells that migrate into this region from their site of origin along the neural axis. Classic tissue recombination experiments have provided evidence of an essential role of the ectoderm in initiating tooth development; however, the underlying ectomesenchyme rapidly acquires dominance in establishing shape. A key question is how these cells acquire this positional information.[18]

One theory suggests that ectomesenchymal cells are pre-patterned with respect to shape generation. Alternatively, this cell population acquires positional information within the first branchial arch itself, following migration. Recent molecular evidence suggests a high degree of plasticity within these ectomesenchymal cells. In particular, signaling molecules within the ectoderm exert a time-dependent influence upon the ectomesenchyme by establishing specific domains of homeobox gene expression. Initially, these ectomesenchymal cells are plastic and able to respond to signalling from the ectoderm, however, this plasticity is rapidly lost and pattern information becomes fixed. Therefore, in the first branchial arch, local regulation between the ectoderm and neural crest-derived ectomesenchyme is crucial in establishing the appropriate tooth shape in the correct region of the jaw.[19]

A molecular model of time-dependent dental pattern generation within CNCC that migrates into the first branchial arch, via early signaling from the overlying ectoderm, is now established. Fixation of this pattern information allows reciprocal signaling from ectomesenchyme to the ectodermal components of the tooth germ during the shape-changing events that leads to the firm establishment of crown and root morphology. Less is known about the mechanisms that regulate different molecular responses within ectomesenchyme derived from the mandible and maxilla. The analysis of how CNCC streams are distributed to discreet areas of the first arch, in particular, the tooth-forming regions and the relative contribution of local cell community signaling within these cell groups, will allow further dissection of the complex molecular processes that give rise to mammalian tooth shape.[20]

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