Head and Neck Development and Malformations

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Learning Objectives

- Learn cranial neural crest cells and their contribution to craniofacial development

- Know the different components of the pharyngeal arch and their later fates, be able to recognize the pharyngeal origin of mature structures, and recognize which structures are non-pharyngeal. Developmental terms from this lecture that are of particular importance: pharyngeal arch, pouch, and cleft, frontonasal process.

- You should be able to recognize the developmental significance of innervation patterns and transitions in terms of the developmental origins of the innervated structures.

- Embryonic basis for cleft lip with or without cleft palate, cleft palate, and other craniofacial malformations.
Neural crest cells

A. Neural folds approaching each other
B. Neural fold
C. Neural groove
D. Neural crest
E. Neural tube
F. Developing spinal ganglion
Cranial neural crest cell migration
CHONDROBLASTS
MELANOBLAST
SCHWANN CELLS
NEUROBLAST
SENSORY NEURON
SYMPATHETIC NEURON
MOTOR NEURON
ECTO-MESENCHYMAL CELLS
FIBROBLASTS
ODONTOBLAST
CHROMAFFIN CELLS
CEMENTOBLASTS
NEURAL CREST CELLS
NEURAL CREST CELLS
Rhombomeres and neural crest cell migration
Pharyngeal arches and their associated cranial nerves
Neural Crest Cell Fate Analysis using DiI injection
Labeling of the cranial nerves
Migration of cranial neural crest cells
Pharyngeal arches

In humans = pharyngeal arches
In fish = branchial arches

Ectoderm separating arches on outside = pharyngeal cleft (or groove)
Endoderm separating grooves on inside = pharyngeal pouch
The pharyngeal arches are fetal structures that constitute most of the nonneural elements of the head and neck. Humans (and other mammals) have **five pharyngeal arches (numbered 1, 2, 3, 4, and 6)**.

A pharyngeal cleft (or groove) separates adjacent arches on the outside (= ectoderm), and a pharyngeal pouch separates adjacent arches on the inside (= endoderm).

In addition to ectoderm and endoderm, each arch has an **artery**, a **nerve**, a **cartilagenous element**, and **mesenchymal cells**.

The **first arch** has two subdivisions: the maxillary process and the mandibular process.

- The trigeminal nerve (the nerve of the 1st arch) has separate branches that innervate each (CNV2 and CNV3 respectively).

The **fron tonosal process** (prominence) (FNP) in the anterior midline is similar to a pharyngeal arch (it has a nerve (CN V1) and mesenchyme and follows a similar developmental strategy) but is somewhat different as well (there is no pouch or cleft that demarks it, and no cartilage).
Pharyngeal arches

(note: 1st arch ectoderm (blue) extends to inside (of what will become the oral cavity))
## Table 10-1: Structures Derived From Pharyngeal Arch Components

<table>
<thead>
<tr>
<th>Arch</th>
<th>Nerve</th>
<th>Muscles</th>
<th>Skeletal Structures</th>
<th>Ligaments</th>
</tr>
</thead>
</table>
| First (mandibular) | Trigeminal† (CN V) | Muscles of mastication‡  
Mylohyoid and anterior belly of digastric  
Tensor tympani  
Tensor veli palatini | Malleus  
Incus | Anterior ligament of malleus  
Sphenomandibular ligament |
| Second (hyoid) | Facial (CN VII) | Muscles of facial expression§  
Stapedius  
Stylohyoid  
Posterior belly of digastric | Stapes  
Styloid process  
Lesser cornu of hyoid  
Upper part of body of hyoid bone | Stylohyoid ligament |
| Third | Glossopharyngeal (CN IX) | Stylopharyngeus | Greater cornu of hyoid  
Lower part of body of hyoid bone | |
| Fourth and sixth | Superior laryngeal branch of vagus (CN X)  
Recurrent laryngeal branch of vagus (CN X) | Cricothyroid  
Levator veli palatini  
Constrictors of pharynx  
Intrinsic muscles of larynx  
Striated muscles of esophagus | Thyroid cartilage  
Cricoid cartilage  
Arytenoid cartilage  
Corniculate cartilage  
Cuneiform cartilage | |

*The derivatives of the aortic arch arteries are described in Chapter 14.†The ophthalmic division does not supply any pharyngeal arch components.‡Temporalis, masseter, medial and lateral pterygoids.§Buccinator, auricularis, frontalis, platysma, orbicularis oris and orbicularis oculi.††The fifth pharyngeal arch is often absent. When present, it is rudimentary and usually has no recognizable cartilage bar. The cartilaginous components of the fourth and sixth arches fuse to form the cartilages of the larynx.
4 of the 12 cranial nerves innervate the pharyngeal arches.

**Pharyngeal arch nerves**

- First arch: Trigeminal (CN V)
- Second: Facial (CN VII)
- Third: Glossopharyngeal (CN IX)
- Fourth and sixth: Vagus (CNX)

***Each pharyngeal nerve is a mixed nerve, with a motor component to pharyngeal muscle cells, and a sensory component to pharyngeal epithelium (ectoderm or endoderm).***
Pharyngeal arch cartilage
Pharyngeal arch muscle

Posterior belly of digastric muscle
Recall the general formation of most body muscles: are derived from paraxial mesoderm -> somites
- myotome -> muscle cells.

- Muscle cells obtain innervation early, and maintain that innervation as they migrate.

- Craniofacial muscles are also derived from paraxial mesoderm, except that somites do not form per se in the head (there is an analogous domain of paraxial mesoderm that is called “somitomeres”, not a term to know). Craniofacial muscles also maintain their early innervation pattern once it is established.

Note that some craniofacial muscles migrate within pharyngeal arches, other do not.

Pharyngeal muscles intermingle and migrate widely though the head and neck. However, the origin of each muscle can always be determined by its innervation pattern.

The origin and innervation of tongue muscles is described below.
## Innervation of cranial muscles

<table>
<thead>
<tr>
<th>Innervation</th>
<th>Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculomotor (III)</td>
<td>Sup, med, inf. recti</td>
</tr>
<tr>
<td>Troclear (IV)</td>
<td>Sup. oblique</td>
</tr>
<tr>
<td>Trigeminal (V)</td>
<td>Muscles of mastication</td>
</tr>
<tr>
<td>Abduccens (VI)</td>
<td>Lat. rectus</td>
</tr>
<tr>
<td>Facial (VII)</td>
<td>Facial (various)</td>
</tr>
<tr>
<td>Glossopharyngeal (IX)</td>
<td>Stylopharyngeus</td>
</tr>
<tr>
<td>Vagus (X)</td>
<td>Palate and Intrinsic laryngeal</td>
</tr>
<tr>
<td>Hypoglossal (XII)</td>
<td>Tongue muscles</td>
</tr>
</tbody>
</table>

(Pharyngeal nerves and muscles in red)
General sensory innervation of oral cavity

Special sensory innervation of tongue

CN VII (trigeminal) to anterior 2/3 of tongue
CN IX and CN X to posterior 1/3

Motor innervation of tongue

CN XII (12) to all tongue muscles except for palatoglossus (CN X)
Craniofacial mesenchyme
a loosely organized, mainly mesodermal embryonic tissue that develops into connective and skeletal tissues, including blood and lymph.

NC gives rise to:
dura of brain
ganglia of cranial nerves

Mesoderm gives rise to:
striated muscle
endothelium

blue = cranial bones of NC origin
red = cranial bones of mesodermal origin

Both give rise to:

Pharyngeal mesenchyme has two developmental origins: mesoderm and neural crest. There are some unique fates for each of these (pharyngeal mesoderm is the source of cranial vascular endothelium and striated...
Migration of cranial neural crest cells and facial development
Normal lip formation
Unilateral and bilateral cleft lip with cleft palate
First arch syndrome

- Defects of external ear
- Mandibular hypoplasia
- Cleft palate (variable)
The anatomy of palatogenesis

6 wks

Nasal cavity
Oral cavity
Tongue

Lateral palatine process
Nasal septum

Maxillary prominence
Mandibular prominence

Medial palatine process
Nasal septum

Lateral palatine process
Nasal septum

7 wks

Incisive papilla
Lip

Hard palate
Soft palate

Nasal cavity
Nasal septum

Primary palate
Secondary palate

Site of incisive foramen
Secondary palate

Fused lateral palatine processes
Tongue

Nasal septum
Nasal cavity
Nasal septum

Bone developing in maxilla

8 wks

Inferior constrictor
Median palatine process

Site of future fusion
Nasal septum

Pharynx
Tongue

Hard palate
Soft palate

Uvula
Nasal cavity
Nasal septum

Incisive papilla
Lip

12 wks

Frenulum of lip
Inferior constrictor

Inferior constrictor
Maxillary prominence

Nasal cavity
Tongue

Nasal septum
Nasal cavity

Bone developing in maxilla
Fused lateral palatine processes

Primary palate
Secondary palate

Nasal cavity
Tongue

Incisive papilla
Lip

Hard palate
Soft palate

Uvula
Nasal cavity
Nasal septum
The oral cavity is delimited by the FNP, maxillary processes, and mandibular processes. The mandibular processes fuse in the midline, the two (bilateral) maxillary processes do not fuse at first and are separated from each other by the distal end of the FNP (the intermaxillary segment). Externally, the FNP is the origin of the philtrum of the upper lip.
Formation of palate
Cleft palate
Cleft palate (histology)
Cleft lip with cleft palate
Tooth Development

- **Initiation Stage**
  - Odontogenic Epithelium
  - Mesenchyme (ecto)
  - Dental Lamina
  - Dental Papilla

- **Bud Stage**
  - Stratum Intermedium
  - Permanent Tooth Root

- **Cap Stage**
  - Successional Lamina
  - Cervical Loop

- **Bell Stage**
  - Dental Papilla
  - Capacitary Invaginations

- **Crown Formation**
  - Ameloblasts
  - Enamel
  - Dentin
  - Odontoblasts
  - Pulp
Molecular Regulation of Tooth Morphogenesis

ACTIVIN
BMP
Barx1
Dlx1
Dlx2
Gli1
Gli2
Gli3
Lhx6
Lhx7
Msx1
Msx2
Pax9

BMP
FGF
Barx1
Cbfal
Dlx1
Dlx2
Gli1
Gli2
Gli3
Lef1
Lhx6
Lhx7
Msx1
Pax9

BMP
FGF
WNT
Barx1
Cbfal
Dlx1
Dlx2
Gli1
Gli2
Gli3
Lef1
Lhx6
Lhx7
Msx1
Pax9

**ds** = dental sac
enamel organ epithelium
inner enamel epithelium
outer enamel epithelium
stellate reticulum

ERUPTION
dentin
pulp
cementum
Formation of tongue (epithelium)

The location of the oropharyngeal membrane represents the transition from ectoderm to endoderm in the oral cavity. This transition lies within the oral cavity, anterior to the 1st pharyngeal pouch. This is also the location of a transition in sensory innervation of the epithelium of the oral cavity from CN V (ectoderm) to CN IX (endoderm).

The anterior 2/3 of the tongue forms from tongue buds derived from the 1st arch (= ectodermal, CN V innervation). Inside the oral cavity, the 3rd arch displaces the 2nd arch to the outside, such that the posterior 1/3 of tongue is derived from the 3rd arch (endodermal, CN IX), with the very posterior end of tongue derived from the 4th arch (endodermal, CN X).
Germ Layer Derivatives

- Ectoderm
- Mesoderm
- Endoderm

Pharyngeal Grooves and Arches:
1. 1st
2. 2nd
3. 3rd
4. 4th

Cervical Sinus:

Pharyngeal Pouches:

Thyroid diverticulum

Tongue buds

External acoustic meatus

Cervical vesicle

Thyroid gland

Thymus

Palatine tonsil

Lymphoid tissue

Skin of neck

Superior parathyroid gland

Ventral parathyroid gland from 3rd pharyngeal pouch

Superior parathyroid gland from 4th pharyngeal pouch

Ultimobranchial body

Tongue

Tympanic cavity and pharyngotympanic tube

Auricle

Foramen cecum

External acoustic meatus

Tympanic membrane

Lymphatic tissue

Skin of neck

Superior parathyroid gland

Inferior parathyroid gland

Tonsillar sinus

Tonsillar sinus

Former site of cervical sinus

Thyroid gland

Thymus

Ultimobranchial body

Thyroid gland

Inferior parathyroid glands

Superior parathyroid glands

Ultimobranchial bodies
Thyroid
Cervical thyroglossal duct cyst

Foramen cecum of tongue

Hyoid bone

Thyroid cartilage

Thyroglossal duct cyst

Opening of thyroglossal duct sinus

Thyroid gland

Lingual thyroglossal duct cyst

Hyoid bone

Cervical thyroglossal duct cyst
Imaging of a thyroglossal duct cyst
Pre-natal Diagnosis

• Ultrasound
  – Level II USN
  – Operator dependent
  – Isolated cleft palate difficult

• Amniocentesis
  – Does not detect isolated CL/CP

• Chorionic Villus Sampling
  – Does not detect isolated CL/CP
Craniofacial Team at CHLA

- Audiologist
- Pediatric Dentist
- Pediatric Pulmonologist
- Pediatrician
- Speech Pathologist
- Orthodontist
- Social Worker
- Pediatric psychologist
- Plastic Surgeon
- Oral Surgeon
- Otolaryngologist
- Craniofacial Nurse
- Geneticist
- Ophthalmologist
Cleft Lip and Palate Patient

- Cleft Lip Repair (3 months old)
- Cleft Palate Repair (1 year old)
- Alveolar bone graft (7 or 8 years old)
- Jaw Surgery (15 to 20 years old)
- Cleft Lip Rhinoplasty (15 to 20 years old)
- Cleft Lip/Nose Revision

Nasoalveolar Molding (2-5 weeks begin)

Pharyngoplasty (speech dependant)

10-15 Team Visits
Repair of cleft lip with or without cleft palate
Nasoalveolar Molding