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Review Article

Embryological development of human parotid gland: A Review

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Abstract

The parotid, submandibular, and sublingual glands are major salivary glands (SG). The parotid gland (PG) is composed mainly of serous acini and produces watery secretion. Development of major SG begins in the human embryo as a result of complex interaction between the oral epithelium and underlying mesenchyme. Parotid bud originates near the angle of the stomodeum at its ectodermal region and grows out laterally towards the otic placode. As bud formation begins, the portion closest to the stomodeum eventually differentiates into the main excretory duct, and the most distal portion of the bud forms the secretory acini. Parotid duct (PD) development begins as an elongated furrow running dorsally from the angle of the mouth, between the mandibular and maxillary prominences of the 1st pharyngeal arch. The size of oral fissure is reduced by partial fusion between the maxillary and mandibular prominences, and the PD opening is found in front of the buccopharyngeal membrane (BPM) on the inner surface of the cheek, which is opposite to the future second upper molar tooth. The buccinator muscle originates from the alveolar process of the maxilla and mandible, and the pterygomandibular raphe and its fibers converge towards the modiolus. In addition, the buccinator may act as a sphincter and play a role in regulating the PD. Embryologically, the development of the parotid gland (PG) is closely associated with the developing buccinator muscle and the derivatives of the first and second pharyngeal arches. The deep part of the gland, situated in the infratemporal fossa, is related to first pharyngeal arch derivatives, including the muscles of mastication and the mandibular division of the trigeminal nerve. In contrast, the superficial part of the gland is associated with second pharyngeal arch derivatives, namely the muscles of facial expression and the facial nerve.

Keywords

Parotid embryology, Buccopharyngeal membrane, Stomodeum, 1st and 2nd pharyngeal arches.

Introduction

There are three pairs of chief salivary glands (SG), namely parotid, submandibular and sublingual glands, with hundreds of minor SG in the oral cavity. SG is an exocrine multi-lobular and compound tubuloacinar gland. Anatomical architecture of major SG is essentially the same. Secretory end pieces produce the saliva. Saliva is a complex mixture of organic and inorganic components and water(1). Saliva lubricates the oral cavity to enable talking, swallowing, eating, tasting, maintaining dental health and oral homeostasis, while also providing protective functions and aiding in digestion. The parotid gland (PG) is composed mainly of serous acini and produces watery serous secretion. (2) Acinar cells are surrounded by an extracellular matrix, myoepithelial cells, myofibroblasts, immune cells, endothelial cells, stromal cells and nerve fibers. Main duct opens into oral cavity and ducts transport and modify saliva before it is excreted into oral cavity.(2) Parasympathetic stimulation results in serous or watery and ion secretion and sympathetic stimulation increases secretion of proteins (2).

Major salivary glands are highly vascularized and innervated. The transverse facial artery and posterior auricular artery provide blood supply to PG. Preganglionic fibers from the glossopharyngeal nerve (nerve of 3rd pharyngeal arch) synapse in the otic ganglion and postganglionic fibers reach the gland

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through the auriculotemporal branch of the mandibular division of the trigeminal nerve (nerve of 1^{st} pharyngeal arch). Autonomic innervation of major salivary glands is important for both their secretion and their development.

Methodology

Previous documented articles related to the development of the parotid gland were employed for this review

Development of major salivary glands in humans begins around 6–8 weeks of gestation. (2) It is a result of a complex interaction between the oral epithelium and underlying mesenchyme (1). Initially, the placodes are formed by thickenings of oral epithelium. It is designed to form a branched glandular structure of ducts with terminal buds, which convert into acini by around the 14^{th} week (2). Epithelial outgrowths, which are of ectodermal origin for the parotid gland, but submandibular gland, and the sublingual gland are of endodermal origin, and minor SG are of mixed ectodermal and endodermal origin (1). Most of Anatomy text books suggested that the parotid is ectodermal, whereas the SMG and sublingual are endodermal. (3) Mesenchymal cells contain information for the branching pattern, whereas epithelial cells carry information for the type of salivary secretions (1,2). PG might arise either from ectoderm, endoderm, or the junction of oral ectoderm with foregut endoderm. During development, this border is marked by the buccopharyngeal membrane. (3)

Formation of the mouth

The buccopharyngeal membrane(BPM) is a bilaminar structure consisting of ectoderm and endoderm. It is a septum between the embryonic mouth(stomodeum) and the primitive pharynx in early embryonic life. An intercalation of ectoderm and endoderm produces the BPM (4). The BPM is attached to the region of the soft palate above, and laterally along the future anterior tonsillar pillars and inferiorly at the junction of the anterior two-thirds and posterior one-third of the tongue. In adult humans, we can notice that the parotid opening(papilla) is found in front of the BPM attachment on the inner surface of the cheek, which is opposite to the second upper molar tooth. The primitive face grows in three dimensions and a stress is placed on BPM and normally BPM breaks down at approximately 4 to.5 weeks' gestation (around 26^{th} day of gestation) and establishing connection between oral cavity and pharynx (5, 6)

In a case of persistent buccopharyngeal membrane, biopsies of BPM shown fat and muscle, with the theory that mesodermal penetration in utero of membrane leads to its persistence. (5)

At the same time, maxillary process and mandibular process are formed by mesenchymal growth of first branchial arch. Stomodeum is surrounded by frontonasal process above, paired maxillary processes on either side, and paired mandibular processes below in early stage. Ventrally, fusion of medial nasal processes with medial maxillary processes will form most of the upper lip and upper jaw on both sides. Fusion of the 2 medial nasal processes displaces the frontonasal process superiorly and posteriorly. Medial migration of maxillary processes is essential to form not only the lateral upper lip but also the upper cheek regions, resulting in continuity of the upper jaw (7)

Gestational period of appearance of salivary glands

The parotid gland originates near the corners of the primitive oral cavity by the sixth week of prenatal life. Submandibular glands arise from the floor of the mouth at the end of the sixth week in utero. The sublingual gland forms lateral to the submandibular primordium at about the eighth week. Buds of minor salivary glands appear from buccal epithelium but after the 12th prenatal week (1)

Thus, the parotid gland (PG) initially arises as an epithelial outgrowth from the angle of the stomodeum and extends laterally toward the otic placode in the region of the petrous part of the temporal bone. Recent genetic lineage-tracing studies have demonstrated that the epithelia of all three major salivary glands are not derived from the endoderm, supporting an ectodermal origin. Salivary gland development is a complex process involving coordinated interactions among multiple cell types, including epithelial, mesenchymal, endothelial, and neuronal cells. Neural crest–derived neuronal precursors aggregate to form the parasympathetic plexus, which surrounds the epithelial stalk that subsequently develops into the major secretory duct. The reciprocal interactions between these cellular components are essential for normal glandular morphogenesis, branching, differentiation, and functional maturation.

Stages of salivary gland formation:

1. **Pre bud stage/ induction of oral epithelium by underlying mesenchyme:** Mesenchyme underlying the oral epithelium induces the proliferation of epithelium, which results in tissue thickening as a placode and bud formation.
2. **Initial bud stage:** is by invagination of thickened epithelium into underlying mesenchyme, which leads to the formation of a spherical bud connected to the oral epithelium through a thick, solid epithelial stalk. The epithelial stalk later gives rise to the main salivary duct.
3. **Early pseudo glandular stage:** Clefts are formed at the surface of the primary epithelial bud, deepen, and divide the primary bud into 2 to 3 buds. These newly formed buds then expand, elongate, and cleft again.
4. **Late pseudoglandular stage:** Branching continues at the terminal portion of the cord, forming an extension treelike system. As branching occurs, connective tissue differentiates around the branches, eventually producing extensive lobulation, which leads to the formation of a multilobed gland.
5. **Canalicular stage:** The SG is initially formed by solid cords of epithelial cells, and later canalization occurs by the sixth month with the formation of a hollow tube or duct to develop a lumen through which future secretory products will be led to the oral cavity. In humans, cavitation occurs at 10 –13 fetal weeks for submandibular glands, at 14 –16 fetal weeks for sublingual glands, and at 16 –18 fetal weeks for parotid glands.
6. **Terminal differentiation stage:** The final stage of SG development is histodifferentiation of functional acini and intercalated ducts. Myoepithelial cells arise from epithelial stem cells in terminal tubules and develop in concert with acinar cytodifferentiation (1).

   Finally, salivary glands consist of acini that drain into intercalated ducts, which convey saliva to the striated ducts. During development, the proximal portion of the epithelial bud differentiates into the main excretory duct, whereas the distal portion gives rise to the secretory end pieces or acini (1)

Parotid duct

The parotid duct (Stensen's duct) originates from the deep lobe of the parotid gland and courses superficially over the masseter muscle, between the upper and lower buccal branches of the facial nerve. It may receive a tributary from an accessory parotid gland before turning medially at a right angle to pierce the buccinator muscle. The duct opens into the oral cavity at the parotid papilla opposite the second maxillary molar tooth. Measuring approximately 5 cm in length, it is formed by the convergence of smaller ducts lined by cuboidal epithelium into larger ducts lined by columnar epithelium. The facial nerve enters the gland through the stylomastoid foramen, traverses its posteromedial aspect, and divides into terminal branches near the anterior border of the gland. Embryological studies have shown that during the formation of the PG, epithelia sprout from angle of mouth reach out back towards the ear. The branches that originated from this sprout later will form communicating smaller ducts (9). According to Hassanzadeh, the parotid gland arises from the epithelial lining of the primitive oral cavity and becomes recognizable at approximately the sixth week of gestation in 8 mm embryos. Development begins as an epithelial groove at the angle of the mouth between the maxillary and mandibular prominences of the first pharyngeal arch. This groove canalizes into a tube that grows dorsally into the surrounding mesenchyme; the tube persists as the parotid duct, while its distal end undergoes branching morphogenesis to form the secretory acini by the tenth week of gestation. Secretory activity begins around the 18th gestational week. As the maxillary and mandibular prominences partially fuse, the oral fissure narrows and the duct opening shifts to its definitive location on the inner cheek (10).

Relationship with the buccinator muscle

Parotid gland development is closely related to the maxillary and mandibular processes of the first pharyngeal arch. Similarly, the buccinator muscle, which arises from the alveolar processes of the maxilla and mandible and the pterygomandibular raphe, converges toward the modiolus at the angle of the mouth, where its fibers blend with those of the orbicularis oris. The buccinator may also function as a sphincter, helping to regulate salivary flow through the parotid duct. Notably, the parotid duct traverses the buccinator muscle before opening into the oral cavity (12). The muscles of facial expression are derived from the mesenchyme of the second pharyngeal arch and are innervated by the facial nerve. It was pointed out in previous studies that small, distinct muscle fibers originating from the buccinator muscle extended to and inserted into the terminal portion of PD. The sequential movements during contraction and relaxation of the buccinator muscle may be transferred to PD through these small muscle fibers, thus regulating the filled and empty states of PG with saliva. Author Hyo-Chang Kang proposed that when the buccinator is relaxed, small muscle fibers that extend to the terminal portion of PD stretch wall of duct in various directions, widening lumen of duct. (13)

Thus, embryologically parotid gland development relates with developing pharyngeal arches of 1^{st} and 2^{nd}. Muscular derivatives of 1^{st} arch mainly muscle of mastication and nerve of 1^{st} arch are located along with deep part of PG in infratemporal fossa and muscular derivatives of 2^{nd} pharyngeal arch such as muscles of facial expression and facial nerve related to superficial part of the PG. Lazaridou et al., (2012) stated that about 75% or more of PG overlies the masseter muscle, while the rest of it is located behind the ramus. (14).

The parotid gland contains several important neurovascular structures, including the facial nerve and its branches, the external carotid artery and its terminal branches, the retromandibular vein and its tributaries, and the auriculotemporal nerve. Its duct opens at the parotid papilla in the oral cavity, opposite the second upper molar tooth, anterior to the embryological buccopharyngeal membrane. The parotid gland is comparatively large and occupies a substantial region superficial to the muscles derived from the pharyngeal arches, whereas other salivary glands associated with the mandibular prominence are smaller. The superficial portion of the gland is enclosed by the deep cervical fascia and parotidomasseteric fascia.

Conclusion

Comparative study of the development of major salivary glands is essential to understand their detail Anatomy, Embryological defects, Histopathological conditions, and its Management.

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