Embryology and development of salivary gland

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ABSTRACT:

Saliva is the mixed glandular secretion which constantly bathes the teeth and the oral mucosa. It is constituted by the secretions of the three paired major salivary glands; the parotid, submandibular and sublingual . Salivary glands are complex in nature. They could be either tubulo acinar, merocrine or exocrine glands secreting mainly saliva. Salivary gland is one of the main soft tissue structures in the maxillofacial area. This review article illustrates the processes that lead to the development,embryology of the salivary glands and how this relates to the adult anatomy.

KEY WORDS: salivary gland embryology, salivary gland development, salivary gland anatomy

INTRODUCTION:

A gland consists of specialized type of cells, wherein they produce products which are used elsewhere in the body. Salivary glands are complex, tubulo acinar, exocrine or merocrine glands secreting mainly saliva. Saliva is the product of the major and minor salivary gland dispersed throughout the oral cavity. It is a complex mixture of organic, inorganic components and water, carrying out several functions. There are three pairs of major salivary glands namely parotid, sub mandibular and sublingual glands in addition to numerous minor salivary glands in the oral cavity[1]. Together these glands produce saliva, which contains digestive enzymes, antibodies, growth factors, and coating substances essential for eating, speaking, tasting, and oral hygiene[2,3].

SALAIVARY GLAND ANATOMY:

The three pairs of major salivary glands in humans are the parotid (PG), submandibular (SMG), and sublingual (SLG) glands. The anatomical architecture of all three glands is essentially the same: an ductal structure that opens into the oral cavity with secretory end pieces, the acini, producing saliva. The acinar cells are surrounded by an extracellular matrix, myoepithelial cells, myofibroblasts, immune cells, endothelial cells, stromal cells, and nerve fibers. The ducts transport and modify the saliva before it is excreted into the oral cavity through the excretory duct[4,5]. The parotid is ectodermal while the submandibular and sublingual glands are endodermal in their origins. The parotid represents the largest of the salivary gland which is situated between the external acoustic meatus between the ramus of the mandible and sternocleidomastoid muscle. Each gland is encapsulated and is composed of fat tissue and cells that secrete mainly the serous fluids. The major duct of each parotid gland is called Stensen’s duct which opens into the vestibule of the mouth opposite the crown of the upper second molar tooth. The parotid gland being primarily serous in secretion secretes watery serous saliva[6]. The submandibular glands are located along the side of the lower jawbone in the anterior part of digastric triangle. Each gland has a major duct called Wharton’s duct which opens on the floor of the mouth, on the summit of sublingual papilla at the side of frenulum of the tongue. Each of these glands is covered by a capsule which gives off mixed serous and mucous secretion in nature. The sublingual glands are the smallest of the major salivary glands which lies above mylohyoid and below the mucosa of the floor of the mouth. They are not covered by a capsule and are therefore more dispersed throughout the surrounding tissue. Their secretions are drained by many small ducts known as Rivinus’s ducts that exit along the sublingual fold at the floor of the mouth. Sometimes, few anterior ducts may join to form a common duct called Bartholin’s duct, their secretion being mixed in nature which empties into Wharton’s duct. The sublingual and minor salivary glands are primarily mucous in nature.

EMBRYOLOGY OF SALIVARY GLAND:

The embryologic development of the salivary glands is the result of a highly orchestrated complex interaction between 2 distinct tissues, the oral epithelium and the underlying mesenchyme. All of the salivary glands share a common embryogenesis in that they develop from growths of oral epithelium into the underlying mesenchyme. The secretory units (acini) and the ductal system of each gland will eventually arise from these epithelial outgrowths, which are of ectodermal origin for the parotid glands, submandibular glands, and sublingual glands, and are of mixed ectodermal and endodermal origin for the minor salivary glands. The mesenchymal cells contain the information for the branching pattern that eventually will be the morphologic signature of these glands, whereas the epithelial cells carry the information for the type of salivary secretions that will be produced by each future gland[7,8]. The stroma, which comprises the capsule of each gland as well as the septae that divide the gland into lobes and lobules will develop from cranial neural crest cells, which are cells that originate from the dorsal part of the neural tube epithelium[9]. Parotid glands are the first to develop from the 6th week of intrauterine life, followed by submandibular in the 7th week, the sublingual in the 8th week, and other minor Salivary Glands during the 9–12th weeks. Whereas parotid and minor SGs are certainly ectodermal in origin, submandibular, and sublingual glands arise from the mouth floor in the junctional regions between ectoderm and endoderm. From 18 to 25th week, Salivary Gland acquire connective capsules and interlobular ducts, while glandular parenchyma shows a rapid growth, leading to highly increase in the number of lobules, and almost complete canalization of the tubules[10,11] . Although the parotid is the first to develop, it is encapsulated after the submandibular and sublingual glands. This delayed encapsulation is critical because lymphatic system develops within mesoderm after encapsulation of the submandibular and sublingual glands but prior to encapsulation of the parotid gland . The distal perforation of the submandibular duct or Wharton duct into the medial paralingual sulcus is believed to be one of the last stages in the Salivary Gland development[12].

DEVELOPMENT OF SALIVARY GLAND:

The development of the glandular tissue involves the interaction of the epithelium with the underlying mesenchyme to form the functional part of the tissue[13,14]. These epithelialmesenchymal interactions are also known as secondary induction in which the mesenchyme is in close proximity with the epithelium and is required for the normal development of the epithelium. For example, epithelial-mesenchymal interactions regulate both the initiation and growth of the glandular tissue and the eventual cytodifferentiation of cells within the salivary glands. The mesenchyme, therefore, is required for normal development as well as formation of the supporting part of the adult gland. All salivary glands follow a similar development pattern. The functional glandular tissue (parenchyma) develops as an epithelial outgrowth (glandular bud) of the buccal epithelium that invades the underlying mesenchyme. The connective tissue stroma (capsule and septa) and blood vessels form from the mesenchyme. The mesenchyme is composed of cells derived from neural crest and is important for the normal differentiation of the salivary glands. As the bud formation begins during development, the portion of the bud closest to the stomodeum eventually differentiates into the main excretory duct of the gland, while the most distal portion of the bud forms the secretory endpieces or acini. The origin of the epithelial buds is believed to be ectodermal in the parotid and minor salivary glands but endodermal in origin in the submandibular and sublingual glands. The parotid gland originates near the corners of the primitive oral cavity by the sixth week of prenatal life. The submandibular glands arise from the floor of the mouth at the end of the sixth or the beginning of the seventh week in utero. The sublingual gland forms lateral to the submandibular primordium at about eighth week. All the minor salivary glands bud from buccal epithelium but start after their 12th prenatal week.

STAGES OF SALIVARY GLAND DEVELOPMENT:

The Initiation of the Salivary Anlagen/Pre bud stage

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Initial bud stage

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Early pseudoglandular stage

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Late pseudoglandular stage

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Canalicular stage

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Terminal differentiation stage

The initiation of salivary analagen/ Pre but stage/ induction of oral epithelium by underlying mesenchyme:

The mesenchyme underlying the oral epithelium induces the proliferation in the epithelium which results in tissue thickening and bud formation. The first sign of salivary gland development consists of a thickening of the oral epithelium, known as the placode or prebud stage. In humans, the parotid anlagen appear first, between the fourth and sixth embryonic weeks, as solid epithelial placodes in the developing cheeks. The placodes for the submandibular glands appear later in the sixth embryonic week in the medial paralingual sulcus. During the seventh to eighth embryonic weeks, the sublingual gland anlagen arise from multiple epithelial placodes, lateral to the submandibular glands, and finally the minor salivary glands develop late in the 12th fetal week .

Initial bud stage:

The prebud stage is followed by an invagination of the thickened epithelium into the 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 will give rise to the main salivary duct, whereas the terminal bulb constitutes the primordium of the intralobular parenchyma. Each epithelial bud is surrounded and separated from the mesenchyme by a basement membrane, which is a thick layer of extracellular matrix that has within it a broad range of structural macromolecules. The basement membrane not only provides structural support to the epithelium, but it acts as a reservoir of growth factors and is actively remodeled during salivary gland development. Concomitant to the downward growth of the epithelial bud, the surrounding mesenchymal cells become more tightly packed and form a well-defined mesenchymal condensation, which will subsequently form the capsule of the gland. This stage is known as the initial bud stage. Fibroblast growth factors (FGF) appear to be essential for the formation of the initial salivary bud[17].

Early pseudoglandular stage:

A solid cord of cells forms from the epithelial bud through cell proliferation. Condensation and proliferation occur in the surrounding mesenchyme which is closely associated with the epithelial cord. The basal lamina plays a role in influencing morphogenesis and differentiation of the salivary glands throughout the development[18].The arborization of the salivary gland epithelium is produced by branching morphogenesis. Clefts form 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, and successive rounds of expansion, elongation, and clefting progressively build up an extensive network of epithelial stalks and end buds. Epithelial growth is supported by a high level of mitotic activity in the epithelial end buds. This stage, known as the early pseudoglandular stage[19].

Late pseudoglandular stage:

Eventually , the elongated network of epithelial stalks and end buds leads to the formation of a multilobed gland.The basement membrane is secreted by the epithelial cells located at the periphery of the salivary epithelial bud and the adjacent mesenchymal cells, whereas the stromal elements of the extracellular matrix are produced by the mesenchymal cells. The branching continues at the terminal portion of the cord forming an extension treelike system of bulbs. As branching occurs, the connective tissue differentiates around the branches, eventually producing extensive lobulation. The glandular capsule forms from mesenchyme and surrounds the entire glandular parenchyma. The basement membrane and stromal extracellular matrix contain a number of molecules, including collagens, fibronectin, proteoglycans, growth factors, and proteases that control the branching process.

Canalicular stage:

Canalization of the epithelial cord, with the formation of a hollow tube or duct, usually occurs by the sixth month in all the major salivary glands. The epithelial tree of the developing salivary glands is initially formed by solid chords of epithelial cells. At approximately the 10th fetal week, these solid chords of epithelial cells start to be hollowed out to develop a lumen through which the future secretory products will be led to the oral cavity[20]. This stage is referred to as the canalicular stage .

The two main theories to explain the mechanism of canalization are:

• Different rates of cell proliferation between the outer and inner layers of the epithelial cord.

• Fluid secretion by the duct cells which increases the hydrostatic pressure and produces a lumen within the cord. Further branching of the duct and structure and growth of the connective tissue septa continues at this stage of development.

The canalization process is mainly driven by differential apoptosis of the central and peripheral epithelial cells. Survivin, an inhibitor of apoptosis, inhibits the action of caspases and is expressed in the outer cells that line the forming ducts, protecting them from apoptosis. The more centrally placed cells are not protected by survivin and thus undergo apoptosis[21]. The canalization process initiates during branching morphogenesis in the most proximal epithelial stalks and spreads toward the most distal structures. At the distal ends of the growing epithelial tree, end buds that undergo branching morphogenesis are protected from canalization by FGFs[22]. Similarly, E-cadherin, an epithelial transmembrane protein involved in cell adhesion, prevents premature lumen formation. Eventually, lumina will form in terminal buds, which will later give rise to the secretory acini of the gland. In humans, cavitation occurs at 10 –13 fetal weeks in the submandibular glands, at 14 –16 fetal weeks in the sublingual glands, and at 16 –18 fetal weeks in the parotid glands[23-25].

Terminal differentiation stage:

The final stage of salivary gland development is the histodifferentiation of the functional acini and intercalated ducts. Myoepithelial cells arise from the epithelial stem cells in the terminal tubules and develop in concert with acinar cytodifferentiation. When the ducts and acini are finally hollowed out, the terminal differentiation stage starts . During this stage, the epithelial cells lining the ducts, tubules, and acini proceed to differentiate both morphologically and functionally. Throughout the glands, the ducts will differentiate into excretory, striated, and intercalated types, whereas the cells within the acini differentiate into serous or mucous secretory cells as well as myoepithelial cells. These changes show that the intercalated ducts lead from the acini to the striated ducts. Although the primary function of the intercalated ducts is primarily the transport of saliva to the striated ducts, together these ducts may modify the salivary contents of electrolytes. This transport of electrolytes is accomplished by using Na-K pumps and Cl-HCO3 pumps. The first salivary secretions are observed during fetal life. Water and electrolytes pass into the acini from a attenuated capillary network surrounding the acini either by simple diffusion or by an active transport mechanism . In the parotid glands, serous secretions commence in the 18th fetal week, whereas, in the submandibular glands, serous secretory activity starts at the 16th fetal week, increases until the 28th fetal week, and then diminishes. These serous secretions contribute to the amniotic fluids and contain amylase and possibly nerve and epidermal growth factors. In contrast, mucous acini develop postnatally[26].

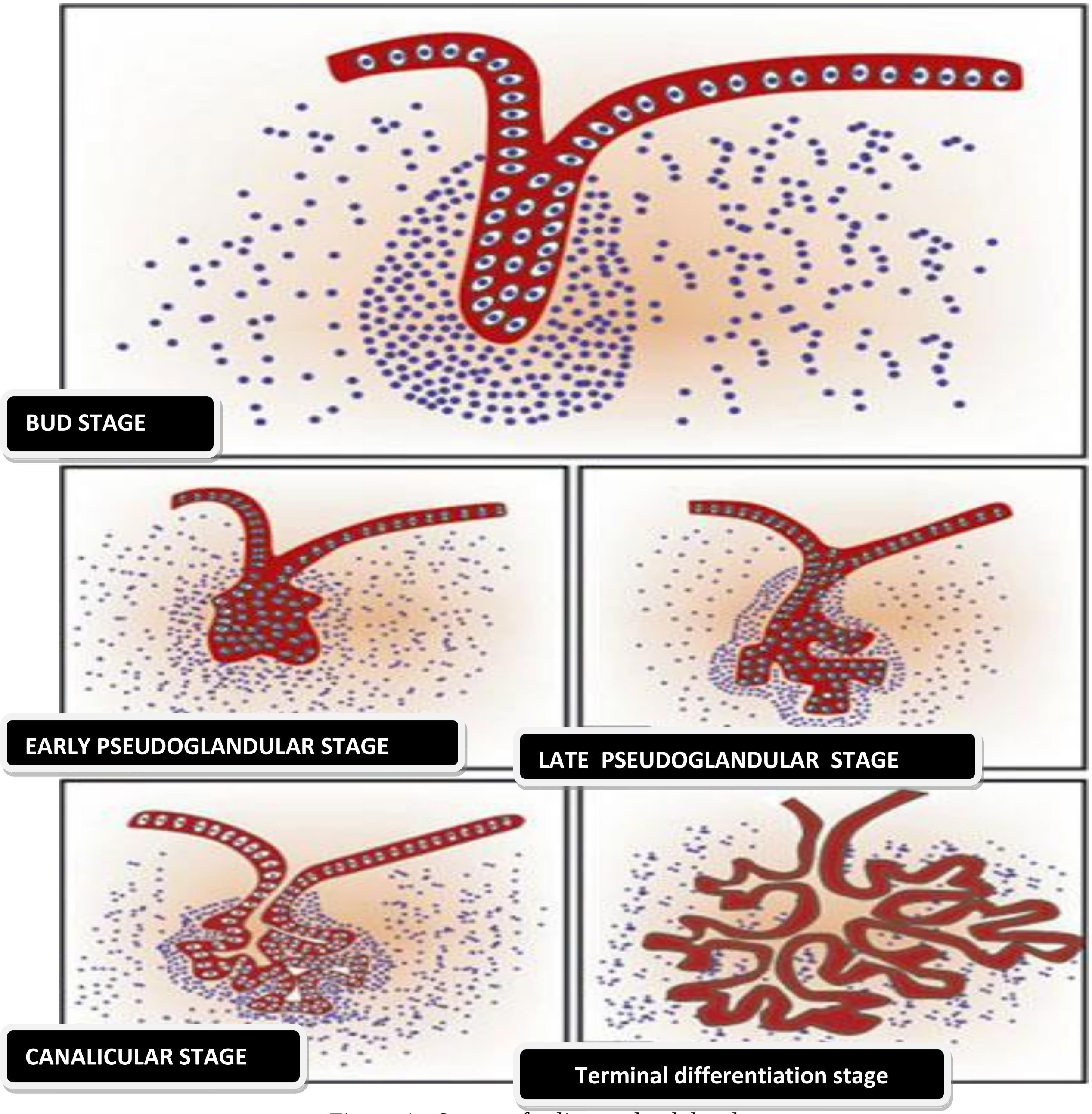

Figure-1 : Stages of salivary gland development

Parasympathetic nerves play an important role in epithelial tubulogenesis in the developing salivary gland which involve epithelial-mesenchymal interaction. The neurotransmitter, i.e., vasoactive intestinal peptide (VIP) and its receptor VIPR1, regulates various steps like epithelial proliferation, duct elongation, and lumen formation through cAMP or protein kinase A (PKA) pathway, thus linking epithelial tubulogenesis with parasympathetic neuronal function. Neurotrophic factor neurturin (NRTN), secreted by the buds, binds its receptor GFR alpha 2 and promotes functional nerve outgrowths to ensure parallel development of nerves and epithelium. Cystic fibrosis transmembrane conductance regulator (CFTR) causes lumen expansion during development [27].

CONCLUSION:

An overview of the development of salivary glands is important in order to understand the physiology, functions and disorders associated with saliva. Salivary glands may be affected by a number of diseases local and systemic and the prevalence of salivary gland diseases depend on various etiological factors one such factor is congenital or developmental disturbances. For better understanding a clear knowledge on the embryology of salivary gland is much required.

REFERENCES:

1. Balogh MB, Margret J, Fehrenbach. Dental Embryology, Histology and Anatomy. 2nd ed. Holland: Elsevier, 2011: 161-168
2. Andrew DJ, Henderson KD, Seshaiah P. Salivary gland development in Drosophila melanogaster. Mech Dev 2000;92: 5–17
3. Miletich I. Introduction to salivary glands: structure, function and embryonic development. Front Oral Biol 2010;14:1–20
4. Carlson GW. The salivary glands: Embryology, anatomy, and surgical applications. Surgical Clinics of North America. 2000; 80:261–273. [PubMed: 10685152]
5. Johns ME. Salivary-glands - anatomy and embryology. Otolaryngol Clin N Am. 1977; 10:261–271.
6. Nanci A. Ten Cate's Oral Histology: Development, Structure, and Function. 7th ed. USA: Mosby, 290-317
7. Kusakabe M, Sakakura T, Sano M, et al. A pituitary-salivary mixed gland induced by tissue recombination of embryonic pituitary epithelium and embryonic submandibular gland mesenchyme in mice. Dev Biol 1985;110:382–91
8. Sakakura T, Nishizuka Y, Dawe CJ. Mesenchyme-dependent morphogenesis and epithelium-specific cytodifferentiation in mouse mammary gland. Science 1976;194:1439 – 41
9. Rothova M, Thompson H, Lickert H, et al. Lineage tracing of the endoderm during oral development. Dev Dyn 2012;241: 1183–91
10. Goldenberg, D., Flax-Goldenberg, R., Joachims, H. Z., and Peled, N. (2000). Misplaced parotid glands: bilateral agenesis of parotid glands associated with bilateral accessory parotid tissue. J. Laryngol. Otol. 114, 883–885. doi: 10.1258/ 0022215001904257
11. Grundfast, K. M., Barber, C. S., and Kubicki, S. P. (1987). Congenital aberrantly located cutaneous Stensen's duct orifice–a newly described anomaly. Int. J. Pediatr. Otorhinolaryngol. 14, 197–202. doi: 10.1016/0165-5876(87)90031-0
12. Amin, M. A., and Bailey, B. M. (2001). Congenital atresia of the orifice of the submandibular duct: a report of 2 cases and review. Br. J. Oral Maxillofac. Surg. 39, 480–482. doi: 10.1054/bjom.2001.0672
13. Cutler LS, Gremski W. Epithelial-mesenchymal interaction in the development of the salivary gland. Critical Reviews in Oral Biology and Medicine. 1991;2(1):1
14. Avery JK. Oral Development and Histology. 3rd ed. BC Decker Inc; 1988. pp. 316-319
15. Batsakis J. Tumor of the head and neck: clinical and pathological considerations. In Batsakis J, ed. Tumors of the Major Salivary Glands. 2nd ed. Baltimore: Williams and Wilkins, 1979:1–120
16. Dardick I, Dardick A, Mackay A, et al. Pathobiology of salivary glands. IV Histogenetic concepts and cycling cells in human parotid and submandibular glands cultures in floating collagen gels. Oral Surg Oral Med Oral Pathol 1993;76: 307–18
17. Ohuchi H. Roles for FGF-FGFR signaling during vertebrate development [in Japanese]. Hum Cell 2000;13:169 –75
18. Patel VN, Rebustini IT, Hoffman MP. Salivary gland branching morphogenesis. Differentiation 2006;74:349 – 64
19. Hsu JC, Yamada KM. Salivary gland branching morphogenesis — recent progress and future opportunities. Int J Oral Sci 2010;2:117–26
20. Tucker AS. Salivary gland development. Semin Cell Dev Biol 2007;18:237– 44

21. Jaskoll T, Chen H, Min Zhou Y, et al. Developmental expression of survivin during embryonic submandibular salivary gland development. BMC Dev Biol 2001:1:5
22. Patel VN, Rebustini IT, Hoffman MP. Salivary gland branching morphogenesis. Differentiation 2006;74:349 – 64
23. Chisholm DM, Adi MM. A histological, lectin and S-100 histochemical study of the developing prenatal human sublingual salivary gland. Arch Oral Biol 1995;40:1073– 6
24. Merida-Velasco JA, Sanchez-Montesinos I, Espin-Ferra J, et al. Development of the human submandibular salivary gland. J Dent Res 1993;72:1227–32
25. Yaku Y. Ultrastructural studies on the development of human fetal salivary glands. Arch Histol Jpn 1983;46:677–90
26. Yaku Y. Ultrastructural studies on the development of human fetal salivary glands. Arch Histol Jpn 1983;46:677–90
27. Nedvetsky PI, Emmerson E, Finley JK, Ettinger A, Cruz-Pacheo N, et al. Parasympathetic innervation regulates tubulogenesis in the developing salivary gland. Developmental Cell. 2014;30:449-462