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The new-fangled conceptual perspectives and advances in the world of salivary gland

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Abstract---Understanding the pathogenesis and being familiar with diagnostic and management methods is critical in order to provide effective oral health care for patients. The current knowledge of the pathogenesis of each cancer subtype has made it possible to classify and define salivary gland tumors better. Specific treatment regimens for salivary gland tumors can be developed by studying molecular biology. Using immunohistochemistry in conjunction with gene analysis using PCR, specific defects can be identified, which provides insight into the most promising therapies. Hypofunctional salivary glands may benefit from organ replacement regenerative therapy using human adult stem cells.

Keywords---salivary gland, tubarial glands, autophagy, personalized therapy, stem cells.

Introduction

In recent decades, huge advances have been achieved in the etiology, diagnosis, and therapy of salivary gland diseases. Recent scientific breakthroughs and technological advancements in the areas of diagnostic markers in salivary gland tumors, aging-related dysfunction in the salivary gland, TGF- β pathway in salivary gland fibrosis, the classification and terminology of salivary gland lesions, novel targets to overcome treatment resistance in advanced stages of salivary carcinoma and previously unidentified bilateral macroscopic Tubarial salivary glands have improved our understanding of disease pathogenesis and modified how we diagnose and treat disease, resulting in more precise, powerful, and predictable healthcare that is tailored to the needs of individual patients.

Diagnostic imaging modality innovation has the potential to improve disease detection and prognosis. As a result, several new molecular alterations are more likely to evolve, potentially increasing the importance of molecular markers. This article aims to provide a comprehensive explanation of novel conceptual advances and viewpoints in the field of salivary glands, which may open up innovative avenues for the prevention and management of various salivary gland disorders.

A previously unnoticed discovery

According to the conventional categorization in anatomy textbooks, there are three sets of large salivary glands: parotid gland around the ears, submandibular gland below the mandible, and sublingual gland under the tongue. Apart from major salivary glands, the oral cavity encompasses a number of minor salivary glands, including lingual, labial, buccal, and palatine glands. These glands are made up of serous, mucous, or seromucous acini that produce saliva of varying viscosity, which is drained into the mouth to facilitate chewing, tasting, swallowing, and maintaining oral hygiene.^{1,2,3}

In the year 2020, the researchers from the Netherlands Cancer Institute (NCI) discovered a bilateral new glandular structure of 4cm in length in the posterior nasopharynx with ligand uptake equivalent to the major salivary glands during a routine screening of 100 prostate cancer patients using positron emission tomography/ computed tomography coupled with radio-labeled ligands to the prostatic specific membrane antigen (PSMA).^{1,4} Because they wrap around the torus tubarius, this fourth pair of salivary glands is known as the "Tubarial glands".^{1,5,6,7,8}

Posterolaterally, these glands showed macroscopic ducts that opened into the pharynx. By pouring secretions onto the dorsolateral wall of the nasopharynx, these glands moisten and lubricate the nasopharynx behind the oropharynx. On histopathological examination, it was found that these glands contained both mucous and serous acini, but primarily mucous acini. The sparing of these tubarial glands has clinical relevance in patients with head and neck cancer, by preventing the incidence of common post-radiation symptoms like xerostomia and dysphagia.^{1, 8, 9} A study was conducted in 2020 by Valstar MH et al to explicate the characteristics and potential clinical implications of these glands and the findings emphasize that preserving these glands from radiotherapy may provide

an opportunity to strengthen patients' quality of life.⁹ Mentis AF et al suggest that tubarial glands may contribute to Upper airway dryness in Sjogren syndrome.¹⁰

Several questions have been raised against the nature of these glands owing to their overlapping spectrum of characteristics.¹¹

1. Is it to be recognized as a major gland?
2. Is it to be regarded as a collection of minor salivary glands?
3. Is it a "macroscopic constituent of the salivary gland system"?
4. Should it be interpreted as a salivary gland?

In clinical practice, the debate is going on for a specific name and identity for this potential structure. Several authors claim that these glands are not considered as salivary glands because their location makes it difficult for their fluids to reach the mouth. Additional research should be carried out to define their exact nature.

Autophagy and salivary gland carcinoma

Salivary gland carcinomas are diverse tumors with varying histological subtypes and a low incidence but a vast range of types. Although there is no specific treatment for salivary gland carcinomas, the outlook is improving with the introduction of new treatment options. Autophagy is a catabolic pathway that performs various cellular functions. This lysosome-dependent process helps to maintain cell homeostasis by regulating cellular degradation and adapting to a wide range of stresses.^{13, 14} Autophagy plays an important but conflicting role in tumor development. It prevents cancerous cells from proliferating during an early phase of carcinoma but allows them to proliferate in the later stages.^{15,16} Numerous clinical trials (Table 1) are currently underway to investigate molecules that modulate autophagy (inducers and inhibitors) at each stage and some of them have yielded promising results in patients with salivary gland carcinoma.

Examples for Autophagy modulators: (Table: 1)

Autophagy activators		Autophagy inhibitors	
1.	MK2206	1.	3-Methyladenine
2.	BKM120	2.	LY294002
3.	Temsirolimus	3.	LY3023414
4.	Rapamycin	4.	Wortmannin
5.	Everolimus	5.	BEZ235
6.	PI- 103	6.	Paclitaxel
7.	Deforolimus	7.	SAR405
8.	Tat-beclin1 peptide	8.	NSC185058
9.	Perifosine	9.	SB203580
10.	Metformin	10.	Sputin-1
11.	GDC-0980/-0941	11.	Verteporfin
12.	Nivolomumab	12.	Bafilomycin A1
13.	Pembrolizumab	13.	Chloroquine
14.	Ipilimumab	14.	Hydroxychloroquine
15.	Cetuximab	15.	Monensin

16.	Panitumumab	16.	Concanamycin A
17.	Fluspirilene	17.	Azithromycin
18.	Isoliensinine	18.	SAHA
19.	Cepharanthine		

Personalized therapy and salivary gland carcinoma

By targeting overexpressed receptors, personalized therapy aims to target chemotherapy or radiotherapy-resistant tumors of the salivary glands.¹⁷ Salivary gland carcinomas are characterized by aberrant expression of v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2/ Human epidermal growth factor receptor 2 (ERBB2/HER2), epidermal growth factor receptor (EGFR), estrogen receptor (ER), or androgen receptor (AR). All of these receptors can be overexpressed in salivary gland carcinomas, but HER2 protein overexpression is most common in salivary duct carcinomas.^{18, 19,20,21,22} Trastuzumab, an anti-HER2 antibody, could be used to treat HER2 3+ overexpressing or HER2 2+ protein-expressing/HER2 gene-amplifying salivary gland carcinomas. Lapatinib, an anti-HER2/EGFR inhibitor, could be useful to manage HER2 and EGFR double-overexpressing carcinomas that do not have EGFR/RAS mutations. In EGFR-mutated/RAS-unmutated carcinomas, Gefitinib may be beneficial, whereas anti-EGFR Cetuximab antibody therapy may be useful in EGFR-overexpressing/EGFR-unmutated/RAS-unmutated cases.^{23, 24, 25, 26} The success of personalized therapies in enhancing patient survival requires more cohort studies. Identifying target factors for heterogeneous salivary gland carcinomas is critical for developing effective therapeutic strategies.¹⁷

Salivary Gland carcinoma and markers

There are different diagnostic markers for different types of salivary gland tumors, allowing for accurate diagnosis in a variety of ways.²⁷ Ki-67 is a prognostic marker that distinguishes benign basal cell adenomas from malignant basal cell adenocarcinomas. Cyclin- and CD43 are also useful markers for the diagnosis of adenoid cystic carcinomas and pleomorphic adenomas. CEA, Cox-1, Cox-2, PGDF beta, WISP-1, and β -catenin may serve as markers to distinguish benign from malignant parotid gland lesions. Adenoid cystic carcinomas possess ductal and myoepithelial /basal cell markers such as CAM 5.2, p63, CK7, calponin, SOX10, SMA, and S100.²⁹ It is possible to detect vimentin, S100, CK AE1/3, EMA, 34BE12, CAM 5.2, p53, and p63 in polymorphous adenocarcinomas.²⁸ Pleomorphic low-grade adenocarcinomas are more easily distinguished from pleomorphic adenomas by GFAP.³⁰ Several markers have been identified in salivary ductal tumors, including GCDFP-15, CK AE1/3, AR, 34BE12, CK7, CEA, and EMA. There are more androgen receptors in salivary duct carcinomas among men than among women.²⁸ Calponin, Mcl-2, NM23, p63, GFAP, S-100, SMA, CD9, and Sox10 are mostly positive in pleomorphic adenomas.²⁷

Recently described salivary gland carcinomas

It has been years since we sought a neoplasm arising in the salivary glands with morphological and immunohistochemical traits very similar to those seen in the Secretory Carcinoma (SC) of the breast. This kind of tumor was previously

classified as either salivary acinic cell carcinoma (AciCC) or cystadenocarcinoma not otherwise specified (NOS) because it was composed of micro-cystic and solid areas with profuse vacuolated colloid-like periodic acid – Schiff (PAS) positive secretory material. Similar to breast secretory carcinomas this entity does have chromosomal translocation t (12; 15) (p13; q25) and fusion of ETV6 and NTRK3.^{31,32,33,34,35} This entity is now known as 'mammary analogue secretory carcinoma (MASC) of the salivary gland' due to its morphological resemblance and the analogy fusion transcript of ETV6 and NTRK3.³⁶

Smith et al. first described 'Sclerosing polycystic adenoma' as 'Sclerosing polycystic adenosis,' and this uncommon salivary gland lesion was initially thought to be reactive or inflammatory. It is now known as sclerosing polycystic adenoma due to its dysplastic to malignant characteristics.^{37,38,39,40,41,42,43,44,45,46,47} 'Cribriform adenocarcinoma of minor salivary glands' (CAMSGs) was initially described by Michal et al as cribriform adenocarcinoma of the tongue in 1999. All of the reported cases have shown neoplasms in the tongue and had similarities to papillary carcinoma of the thyroid gland. As a result, it was believed that this neoplasm could arise from lingual thyroglossal duct remnants. Recent cases showed identical tumors at other oral cavity sites, including the soft palate, retromolar region, lip, and buccal mucosa. Hence this tumor has been re-designated as cribriform adenocarcinoma of minor salivary glands.^{48, 49,50}

The effects of aging on salivary gland structure

Study results have demonstrated aging-related degeneration in the salivary gland parenchyma structures, and this may impede salivary gland function. There is an approximately 30% reduction in the volume of acini in the submandibular glands, nearly 25% in the labial salivary glands, and about 12% in the parotid glands with aging. Aging is also associated with an increase in fibrotic tissue buildup and lipid droplet infiltration in the salivary gland. There is a major increase in the number of extra-lobular ducts in the submandibular glands by 80%, a drop in the striated duct volume from 60% to 40%, and an increase in the non-striated duct volume.⁵¹ Several bodily changes can also be linked to salivary gland dysfunction, such as a decrease in the number of receptors, which will greatly decrease the amount of stimulation the salivary gland receives. In the elderly, factors such as reduced blood flow, impaired neuronal transmission, and medication use can all affect salivary gland function.^{52, 53}

Salivary Gland Fibrosis and the TGF- Pathway

Fibrosis of the salivary gland can be caused by a variety of conditions, including ductal obstructions, infections, chronic inflammation, autoimmune diseases, radiation, and aging.^{54, 55, 56} TGF-1 has been linked to the pro-fibrotic pathogenesis of sialadenitis, Sjögren's syndrome and, post-radiation salivary gland dysfunction. Preclinical and clinical research on promising clinical interventions targeting various stages of the TGF- pathway has already been initiated for the treatment of fibrosis.⁵⁷

Protective role of Epigallocatechin-3-Gallate against radiation-induced salivary tissue injury

Amifostine is a less hopeful therapeutic medicine because of the high prevalence of side effects, the high cost, and the lack of efficacy from several clinical trials. Hence, newer pharmaceuticals are needed to avoid salivary gland damage and preserve the salivary acinar epithelial and stem/progenitor cell populations.^{58, 59} Antioxidant compounds may be useful in protecting normal cells from radiation-induced salivary gland damage. Epigallocatechin-3-gallate (EGCG) is known for its antioxidant and cytoprotective properties. In 2021, Sulistiyani E et al. conducted a study to determine the efficacy of EGCG in radiotherapy patients. The study found that EGCG caused epithelial progenitor cells to increase because of its antioxidant properties that prevented epithelial apoptosis in those patients.⁵⁹

Role of saliva in COVID-19 infection

For SARS-CoV-2, the ACE2 protein acts as a receptor.⁶⁰ ACE2 over-expression was observed in the minor salivary glands when compared to lungs in patients with COVID-19 infection. Therefore salivary glands are regarded as a target organ for early detection of disease before respiratory symptoms manifest.^{61, 62} At a concentration of 1 fg/mL in phosphate-buffered saline, the SARS-CoV-2 spike protein can be detected by an extremely sensitive immunological diagnostic device, the Field Effect Transistor COVID-19 biosensor.⁶³

Stem cells in the salivary gland tissue regeneration

Salivary glands in head and neck cancer patients undergoing radiotherapy may be damaged as a result of irradiation side effects, resulting in decreased saliva production. For these patients, stem cell therapy is an appealing option for regenerating the irradiated salivary gland. Human adult stem cells can regenerate functional salivary gland tissue in patients with radiation or chemotherapy-induced salivary gland damage.^{64, 65}

Conclusion

Broadening the research scope is mandatory to comprehend concepts related to troublesome clinical and anatomical questions concerning the etiopathogenesis, diagnosis, and treatment of salivary gland disorders.

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