Journal of Molecular Histology (2020) 51:109–115
https://doi.org/10.1007/s10735-020-09871-y

REVIEW PAPER

Molecular chaperones in tumors of salivary glands

Charbel A. Basset[1] · Francesco Cappello[1,2,3] · Francesca Rappa[1] · Vincenzo Luca Lentini[4] · Abdo R. Jurjus[5] · Everly Conway de Macario[2,6] · Alberto J. L. Macario[2,6] · Angelo Leone[1]

Received: 29 January 2020 / Accepted: 8 April 2020 / Published online: 16 April 2020

Abstract
The salivary glands are key components of the mouth and play a central role in its physiology. Their importance may be appreciated considering their number, occurrence in pairs, and distribution in the mouth: two parotids, two submandibular, two sublingual, and many other small ones scattered throughout the mouth. They produce saliva, without which ingestion of non-liquid nutrients and speech would be practically impossible. Nevertheless, the physiology and pathology of salivary glands are poorly understood. For instance, tumors of salivary glands occur, and their incidence is on the rise, but their etiology and pathogenesis are virtually unknown, although some risk factors have been identified. Likewise, the role of the chaperoning system in the development, normal functioning, and pathology, including carcinogenesis, remains to be determined. This scarcity of basic knowledge impedes progress in diagnosis, disease monitoring, and therapeutics of salivary gland tumors. We are currently involved in examining the chaperoning system of human salivary glands and we performed a search of the literature to determine what has been reported relating to oncology. We found data pertaining to six components of the chaperone system, namely HSP27, HSP60, HSP70, HSP84, HSP86, and GRP78, and to another HSP, the heme-oxygenase H-O1, also named HSP32, which does not belong in the chaperoning system but seemed to have potential as a biomarker for diagnostic purposes as much as the HSP/chaperones mentioned above. The reported quantitative variations of the six chaperones were distinctive enough to distinguish malignant from benign tumors, suggesting that these molecules hold potential as biomarkers useful in differential diagnosis. Also, the quantitative variations described accompanying tumor development, as observed in cancers of other organs, encourages research to elucidate whether chaperones play a role in the initiation and/or progression of salivary gland tumors.

Keywords Salivary glands · Tumors · Chaperoning system · Molecular chaperones · HSP · Differential diagnosis · Tumorigenesis

✉ Angelo Leone
angelo.leone@unipa.it

1 Department of Biomedicine, Neuroscience and Advanced Diagnostics, Institute of Human Anatomy and Histology, University of Palermo, Palermo, Italy

2 Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy

3 Department of Biology, College of Science and Technology, Temple University, Philadelphia, PA, USA

4 Unit of Pathology, Ospedali Riuniti “Villa Sofia-Cervello”, Palermo, Italy

5 Department of Anatomy, Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

6 Department of Microbiology and Immunology, School of Medicine, University of Maryland at Baltimore-Institute of Marine and Environmental Technology (IMET), Baltimore, MD, USA

Introduction

The salivary glands are the oral cavity’s exocrine glands that synthesize, modify, and secrete saliva (Kessler and Bhatt 2018). Tumors of the salivary glands constitute a rarity among neoplasias (Siegel et al. 2017). With the advancement in modern medicine and the use of imaging techniques in diagnosing patients, and lately with X-ray imaging being more frequently implemented in dental medicine, an alarming increase in salivary gland tumors incidence is occurring annually (Del Signore and Megwalu 2017; Spitz et al. 1990). As the etiology and the mechanism of salivary glands neoplasia formation are ambiguous and not very well understood, it becomes imperative to identify its mode of action and the key molecules participating in the process of neoformation.

Heat shock proteins (Hsps) are evolutionarily conserved molecules that typically participate in anti-stress mechanisms as part of the chaperoning (chaperone) system (Macario and Conway de Macario 2019). This system is composed of molecular chaperones, co-chaperones, chaperone co-factors, and chaperone receptors and interactors. Some molecular chaperones are Hsp, a name derived from the original observation that they are encoded in genes inducible by heat shock. The canonical function of chaperones pertains to maintenance of protein homeostasis; for example, they assist in the proper folding of nascent polypeptides so these can reach their native functional state, protect the cell from stress-induced injury by preventing misfolding or aggregation of misfolded proteins, and promote proteolytic degradation of unstable proteins. Molecular chaperones also display non-canonical functions, unrelated to protein homeostasis, pertaining to their roles in inflammation, immune responses, and many other physiological and pathological processes.

This review, the first on its topic, focuses on the reported quantitative patterns of the molecular chaperones HSP27, HSP60, HSP70, HSP84 (HSP90AB1), HSP86 (HSP90AA1), and GRP78 (HSPA5) and the heat shock proteins heme oxygenases HO-1 and HO-2, which are not molecular chaperones, in salivary gland tumors. The main objective was to determine whether there is information indicating that the molecules mentioned above show quantitative patterns distinctive of gland and tumor type, e.g., benign vs. malignant, with potential in differential diagnosis, and in monitoring patients. It is also expected that the information available will provide clues about the possible participation of molecular chaperones in carcinogenesis in salivary glands and, if the clues are positive, encourage research on the role of chaperones in carcinogenetic mechanism in human salivary glands.

Overview of tumors of the salivary glands

Salivary glands: components and function

The salivary glands comprise various types of glands classified into two main groups, major and minor. The major salivary glands occur in pairs and include the parotid, submandibular, and sublingual glands. The minor salivary glands are scattered throughout the mouth, reaching down to the upper limits of the respiratory and digestive tracts.

The importance of the salivary glands derives from their providing saliva to the oral cavity, which is essential for the physiology of this anatomic region. Human salivary glands secrete between 0.5 and 1.5 L of saliva, daily. Saliva has various key functions, for instance to: (i) start digestion of starches and triglycerides in the mouth cavity through the action of amylases and lipases, respectively; (ii) lubricate food, facilitating its mastication and swallowing; (iii) provide an aqueous medium necessary for taste; (iv) lubricate the buccal mucosa, facilitating speech; and (v) protect against dental caries and chronic buccal mucosal infections (Acharya and Mandal 2016; Carpenter 2013).

The parotid is the largest of the three major salivary glands and is located between the sternocleidomastoid and the masseter muscles (Ellis 2012). The submandibular gland is the second largest with half the weight of the parotid and is found below the mandible. The smallest among the major glands is the sublingual gland, spread in the submucosa in the floor of the mouth, anterior to the deep portion of the submandibular gland (Ellis 2012).

Epidemiology and etiology of tumors of the salivary glands

Tumors of the salivary glands constitute a heterogeneous group according to the WHO Classification of Salivary Glands Tumors of 2005, with a range of different histopathological and clinico-pathological features depending on their type (Seethala and Stenman 2017).

Malignant tumors of the salivary glands are uncommon, but their frequency is steadily increasing. They constitute 5% of the head and neck cancers. In the United States, the incidence is 1.7 per 100,000, being more frequent in older individuals (Siegel et al. 2017). Worldwide, the incidence ranges from 0.5 to 2 per 100,000 (Parkin et al. 2010). The incidence of major salivary gland tumors increased from 1973 to 2009 in the United States by 54% in both, men and women. This increase was mainly observed for malignant tumors of the parotid and for the smaller subset of submandibular glands (Del Signore and Megwalu 2017). An annual rise of 2.5% of major salivary gland malignant tumors between the years 1990 and 2013 has been reported in England (Girdler et al. 2016). Tumors affect more often the major than the minor salivary glands, being more frequent in the parotid (68–84%) than in the submandibular (10–25%) glands (Galdirs et al. 2019; Trenkić Božinović et al. 2015). Most salivary gland tumors in humans have an epithelial origin, 65 to 87% of them being benign (Araya et al. 2015; Bello et al. 2012; Tabatabai et al. 2015; Trenkić Božinović et al. 2015).

The etiology of the tumors of salivary glands has not been much studied and remains to be elucidated. There are various risk factors underpinning salivary gland tumors. The most commonly studied and best-established risk factor is radiation exposure with positive correlation between neoplastic growth and radiation doses (Spitz et al. 1990). X-ray exposure caused by the various medical and dental interventions in the mouth and the head and neck has been implicated since many years ago (Mancuso and Brennan 1970; Radoï et al. 2018; Saku et al. 1997; Schneider et al. 1977).

These observations become pertinent nowadays, considering the exponential increase of X-ray imaging in clinics, particularly in oral surgery and odontology. Nitrous compounds tend to increase the risk of salivary glands tumors (Ho et al. 2011). Prior history of lung, prostate, breast, and lip cancer as well as Hodgkin's lymphoma are also considered risk factors (Dong and Hemminki 2001; To et al. 2012).

Molecular chaperones potential key players in salivary glands tumors development and progression

Molecular chaperones in disease and pathology

As mentioned above, many but not all chaperones are Hsp. Nevertheless, both words are used as synonyms, and we will follow this usage here. Molecular chaperones/Hsp are classified into six groups according to their molecular weight, encompassing the following ranges in kDa: > 200, 100–199, 81–99, 65–80, 55–64, 35–54, and < 34 (Macario et al. 2013). Within these ranges are families of phylogenetically related proteins such as Hsp90, Hsp70/DnaK, Hsp60, Hsp40/DnaJ, and small Hsp, whose names reflect their molecular weight (Cappello et al. 2019).

Although chaperones are typically cytoprotective, they can also be pathogenic and lead to disease (Macario et al. 2013). Diseases in which chaperones act as a primary or auxiliary etiopathogenic factor are called chaperonopathies. Chaperonopathies can be genetic due to alteration of the chaperone gene, by mutation for instance, or acquired, in which a normal chaperone protein is altered due to post-translational modifications, for example (Macario et al. 2013). In addition, normal chaperones (at least as far as it can be determined by the methods at our disposal today), can be recruited by malignant cells to their own advantage and participate in the carcinogenetic pathway; in this case, the chaperonopathy is termed "chaperonopathy by mistake" (Macario et al. 2013).

One of the main partners of the chaperone system that participates in its non-canonical functions is the immune system, and this may lead to another example of chaperonopathy by mistake, as illustrated by the autoimmune response anti-HSP60 in Primary Sjögren's syndrome of the salivary glands (Cappello et al. 2019; Macario et al. 2013).

Molecular chaperones show distinct patterns in tumors of salivary glands and actively participate in their tumorigenesis

Molecular chaperones/HSPs have been found increased in many tumors as mentioned in "Molecular chaperones in disease and pathology" section (Rappa et al. 2014; Sangiorgi et al. 2017), and here we include information pertinent to tumors of the human salivary glands.

HO-1 is also named HSP32 and, together with HO-2, mediates the physiological oxidation and degradation of heme into carbon monoxide, iron, and biliverdin, but are not part of the chaperone system. HO-1 was shown to be strictly localized in the ducts of normal salivary glands and in their tumors. HO-1 is abundant in the luminal cells of the ducts in normal parotid glands. Its levels, as assessed by immunohistochemistry, in the cytoplasm of the cells in the differentiated tumor ducts of pleomorphic adenoma (PA) was increased while there was no marked difference between the normal and tumoral parenchyma, Table 1. The increase in HO-1 in PA could be the consequence of a prior upregulation of the HO-1 gene in the prospective neoplastic ducts lasting into the neoplastic state.

HO-2 is abundant in all the compartments of normal parotid gland, including the ducts and acini. In contrast, in PA, HO-2 was diminished by comparison with normal parotid, and its presence was restricted to the ducts. These HO-2 changes in quantity and distribution pattern may be caused by an increase in nitric oxide (NO) in PA (Lo et al. 2005).

The levels of five HSP/chaperones (HSP27, HSP60, HSP70, HSP84, and HSP86) were assessed by immunohistochemistry in 81 cases of salivary gland tumors, Table 1 (Wang et al. 2013). The aim of the study was to determine if there were differences between benign and malignant tumors and the results did demonstrate differences. HSP27 levels were significantly lower in malignant compared to benign tumors, and negatively correlated with the age of the patients, and tumor proliferation index and size.

HSP60 showed no significant difference between the benign and malignant tumors, Table 1.

Contrary to HSP27 and HSP60, the levels of HSP84, HSP86, and HSP70 were considerably higher in malignant than in benign tumors, and positively correlated with patients age, tumor size and proliferation index, neural invasion, and metastasis, Table 1. Within the benign tumors, HSP84 and HSP86 levels were higher in mixed tumors compared to adenolymphomas and other benign tumor types. The localization of these five HSPs was also reported (Wang et al. 2013): HSP27, and HSP60 were strictly localized in the cytoplasm of the tumor epithelium and in the lower and upper portion of the epithelium, respectively. In contrast, HSP70, HSP84, and HSP86 were not restricted to the cytoplasm but were also localized in the nucleus (Wang et al. 2013).

As stated above, HSP27 was increased in benign tumors (Wang et al. 2013) but it was decreased in PA, Table 1 (de Siqueira et al. 2015). HSP27 may have an antiapoptotic effect and play a protective role as suggested by the mRNA Bcl_2/Bax ratio (antiapoptotic index). It could very well be

Table 1 Examples of studies in which HSPs have been measured in salivary gland tumors

Gland	n	Tumor	HSP	Status	Ref.
Parotid	12	PA (benign)	HO-1	Increased	Lo et al. (2005)
			HO-2	Decreased	
Submandibular	N.A.	HSG Cell line (malignant)	HSP27[a]	Decreased	Aiko et al. (2002)
Parotid	9	PA (benign)	HSP27	Decreased	de Siqueira et al. (2015)
Submandibular	5				
Minor	4				
Parotid	64	Mixed tumors (benign), Adenolymphoma (benign), Others (benign), Mixed tumors (malignant), ACC (malignant), MEC (malignant), Others (malignant)[b]	HSP27, HSP60, HSP70, HSP84, HSP86	HSP84, HSP86, HSP70: increased in malignant. HSP27: decreased in malignant. HSP60: no difference between benign and malignant.	Wang et al. (2013)
Submandibular	7				
Small	10				
Not named	25	PA	HSP27 HSP60 HSP70	Not specified	Yamaguchi et al. (2004)
Minor	41	ACC	HSP27	Increased	Chen et al. (2018)
Major	26				
Parotid	9	PA, MEC, Acinic Cell Carcinoma (malignant)	GRP78	Increased	Bachar et al. (2014)

n number of cases, *Ref.* reference, *PA* pleomorphic adenoma, *N.A.* not applicable, *HSG* human submandibular gland, *ACC* adenoid cystic carcinoma, *MEC* mucoepidermoid carcinoma

[a]See Fig. 1 for proposed mechanisms of participation of HSP27 in carcinogenesis of salivary glands

[b]The authors did not specify to which glands belonged the tumors listed.

that a decrease in HSP27 in PA makes the gland more sensitive to cellular stress and, therefore, facilitates tumor initiation (de Siqueira et al. 2015). The antiapoptotic and protective roles of HSP27 against cell damage were revealed by its direct association with inhibition of cytochrome c-depended apoptosis, which is mediated by the activation of the caspases 3 and 9 pathways, in the human submandibular salivary gland ductal cancer cell line (HSG-DCCL) (Aiko et al. 2002). Moreover, treatment of HSG-DCCL cells with concanamycin A, which activates the release of cytochrome c in the cytoplasm, decreased HSP27 levels and increased subsequent apoptosis (Aiko et al. 2002).

Another study pinpointed the localization of HSP27, HSP60, and HSP70 in PA (Yamaguchi et al. 2004). HSP27, and HSP60 were observed in the cytoplasm of the neoplastic epithelial cells but were not present in the stroma. HSP70 was localized in both the cytoplasm and the nuclei of neoplastic cells (Yamaguchi et al. 2004).

HSP27 was increased in adenoid cystic carcinoma (ACC) in vitro, in a murine model and in human tumor tissues (Chen et al. 2018). The possible deleterious effect of HSP27 was suggested by the diminution of the epithelial marker E-cadherin and the simultaneously increase of the mesenchymal markers Vimentin and N-cadherin combined with the subsequent increase of the mesenchymal transcription factors Prxx1, c-kit, snail1, and Slug. All these data implicate HSP27 in the epithelial-mesenchymal transition (EMT) characteristic of malignancy. Moreover, HSP27 increased the invasiveness and migration of ACC cells accompanied by an increase in radio -resistance in an ACC cell line and in patients with recurrent tumors (Chen et al. 2018). HSP27 seemed to orchestrate the TGF-β-dependent and TGF-β-independent EMT in ACC cells (Chen et al. 2018).

GRP78 is a central regulator of the unfolded protein response in the endoplasmic reticulum (Pfaffenbach and Lee 2011). Under stress conditions, intracellular GRP78 translocates to the cell surface and functions as a signaling receptor, including regulation of tumor cell signaling (Ni et al. 2011). A body of evidence suggests an increase in cell surface GRP78 in tumor cells and this increase has been associated with a greater tumorigenicity, Table 1, (Daneshmand et al. 2007; de Ridder et al. 2011; Fu et al. 2007; Scriven et al. 2009; Zhang et al. 2007). Likewise, cell surface GRP78 was increased in all malignant but not in benign parotid tumors (Bachar et al. 2014). An increase of GRP78 confers resistance to malignant cells against apoptosis (Bachar et al. 2014).

Conclusions and perspective for the future

Salivary glands are key elements in oral physiology and their diseases are an important component of human pathology as evidenced, for instance, by the occurrence of benign and malignant tumors, which is steadily increasing. Unfortunately, despite the findings about molecular alterations in salivary gland tumors mentioned in the literature, there is no definite and complete understanding regarding the etiology

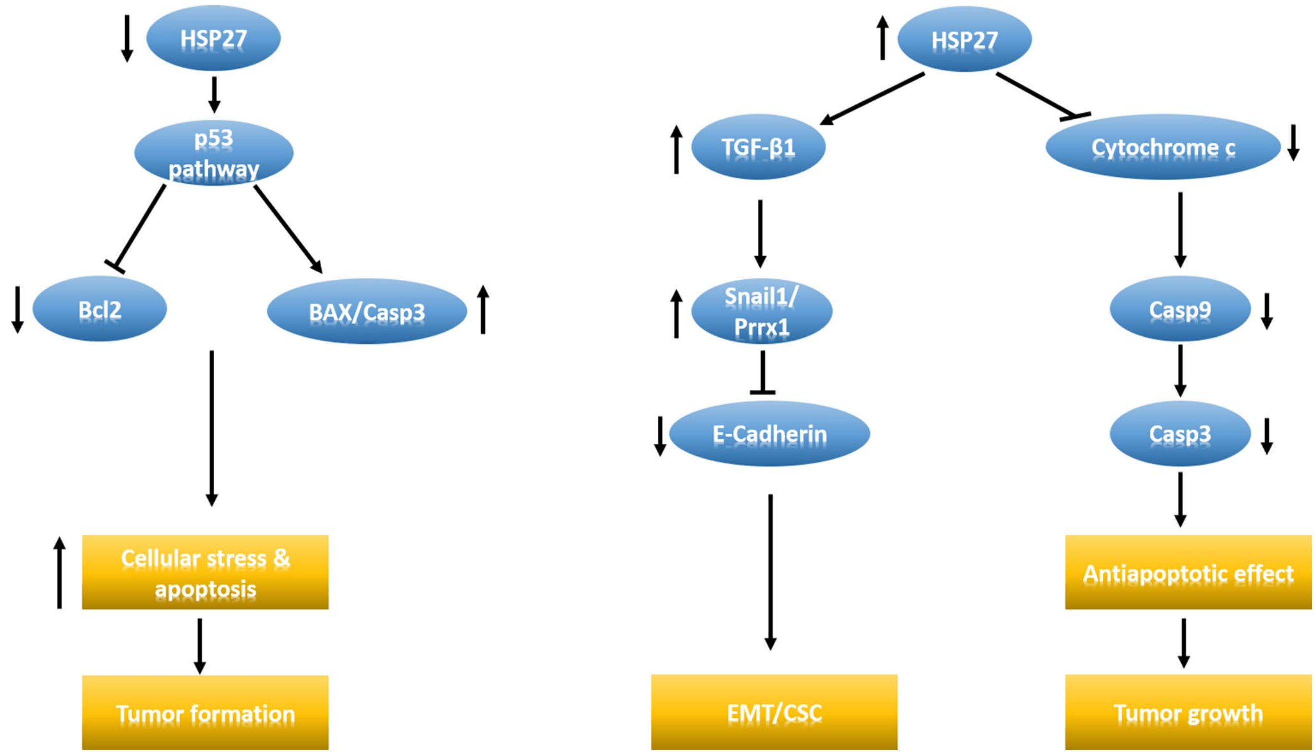

Fig. 1 Proposed pathways involved in the HSP27-dependent tumor progression of salivary glands. HSP27 is typically cytoprotective against cytotoxic stress by inhibiting p53-induced apoptosis. In salivary gland pleomorphic adenoma (left-hand side of the figure), HSP27 decreases, allowing the activation of the p53 pathway, promoting the transcription of downstream pro-apoptotic genes Bcl2-associated X protein (BAX) and caspace-3 (Casp3) and, simultaneously, inhibiting the transcription of antiapoptotic gene Bcl2. As a result, both cellular stress and consequent injury increase, promoting apoptosis and creating a convenient environment for tumor formation. In contrast, in other pathologies, notably adenoid cystic carcinoma (right-hand half of the figure), HSP27 tends to increase, inhibiting mitochondrial cytochrome c release in the cytosol. Inhibition of cytochrome c blocks the activation of caspase-9 (Casp9) and its downstream effector Casp3, downregulating apoptosis and promoting malignancy. HSP27 through the TGF-β1 pathway activates the transcription of epithelial-mesenchymal transition (EMT) transcription factors Snail1 and Prrx1, which inhibits E-cadherin (loss of E-cadherin is a known hallmark of EMT) thus inducing EMT and cancer stem cell (CSC)-like phenotype and promoting malignancy progression.

and mechanisms of these tumors, particularly in what concerns the role that molecular chaperones might play in carcinogenesis in these glands. Malfunctioning of the chaperoning system may play a role in tumorigenesis in salivary glands since some HSPs that are part of the system have been implicated in carcinogenesis in other organs, in which an increase in HSP/chaperones was associated with tumor initiation and progression, and sometimes with poor prognosis and bad response to anti-cancer treatment. To determine if similar data are available for tumors of the salivary glands, we carried out a literature search. We found that the quantitative patterns of six HSP/chaperones reported for various types of salivary gland tumors, benign and malignant, have distinctive characteristics that could help in differential diagnosis and patient follow up. We also discuss reports on two heme oxygenases, HO-1 and HO-2, because the former is a heat shock protein (although not a chaperone) and both have been implicated in some malignancies. HO-1 was strictly located in the ducts of normal salivary glands whereas HO-2 was found in ducts and acini. HO-1 abundance decreased whereas HO-2 increased in PA. HSP70, HSP84, and HSP86, were increased in salivary gland malignant as compared to benign tumors, while HSP27 was elevated in PA. In malignant tumor cells, GRP78 increased, perhaps indicating cellular resistance against apoptosis, whereas the increase of HSP27 in ACC cells may be the mark of the invasiveness and migration characteristic of endothelial-mesenchymal transition. In contrast, HSP27 decreased in other types of salivary gland malignant tumors, reinforcing the idea that HSP quantitative patterns may be distinctive of tumor type. The information we found suggests also that chaperones in salivary glands play key roles under physiological conditions as illustrated, for instance, by data showing that HSPs are more abundant in the ducts than in the acini, a distribution pattern that may indicate that HSPs are involved in saliva modification prior to secretion.

All the information available encourages research aiming at elucidating the real potential of HSP/chaperones as disease biomarkers with clinical applications for diagnosing and monitoring salivary gland tumors. Also, the data suggest that HSP/chaperones play a role in the mechanism of salivary gland carcinogenesis, as found for other tissues. Consequently, research on carcinogenesis in salivary gland should include examination of the possible role of HSP/chaperones. This will also open avenues for developing therapies centered on HSP/chaperones, namely chaperonotherapy. This can be positive if the chaperone is found to have anti-tumor activity but functionally low and should include administration of the chaperone as protein or gene. Also, in this case, boosting the activity of the chaperone with chemical compounds would be another therapeutic strategy. On the contrary, if a chaperone is found to be pro-carcinogenic, negative chaperonotherapy would be indicated. This may consist of blocking the chaperone activity with chemical compounds or blocking production of the chaperone using any of the molecules now known to inhibit gene transcription and mRNA translation.

Acknowledgements A.J.L.M, and E.C. de M. were partially supported by IMET. This work was done under the agreement between IEMEST (Italy) and IMET (USA). This is the IMET contribution number: IMET 20-005.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval for studies involving animals This article does not contain any studies with animals performed by any of the authors.

References

Acharya S, Mandal P (2016) Salivary IgA and dental caries in HIV patients: a pilot study. J Indian Soc Pedod Prev Dent 34(4):341

Aiko K, Tsujisawa T, Koseki T et al (2002) Involvement of cytochrome c and caspases in apoptotic cell death of human submandibular gland ductal cells induced by concanamycin A. Cell Signal 14(8):717–722

Araya J, Martinez R, Niklander S et al (2015) Incidence and prevalence of salivary gland tumours in Valparaiso, Chile. Med Oral Patol Oral Cir Bucal 20(5):e532–e539

Bachar G, Raiter A, Gilat H et al (2014) Apoptosis and cell surface GRP78 expression in benign and malignant parotid gland tumors. Head Neck Oncol 6(2):15

Bello IO, Salo T, Dayan D et al (2012) Epithelial salivary gland tumors in two distant geographical locations, Finland (Helsinki and Oulu) and Israel (Tel Aviv): a 10-year retrospective comparative study of 2,218 cases. Head Neck Pathol 6(2):224–231

Cappello F, Mazzola M, Jurjus A et al (2019) Hsp60 as a novel target in IBD management: a prospect. Front Pharmacol 10:26

Carpenter GH (2013) The secretion, components, and properties of saliva. Annu Rev Food Sci Technol 4(1):267–276

Chen W, Ren X, Wu J et al (2018) HSP27 associates with epithelial-mesenchymal transition, stemness and radioresistance of salivary adenoid cystic carcinoma. J Cel Mol Med 22(4):2283–2298

Daneshmand S, Quek ML, Lin E et al (2007) Glucose-regulated protein GRP78 is up-regulated in prostate cancer and correlates with recurrence and survival. Hum Pathol 38(10):1547–1552

de Ridder G, Ray R, Misra UK et al (2011) Modulation of the unfolded protein response by GRP78 in prostate cancer. Methods Enzymol 489:245–257

de Siqueira EC, Souza FTA, Diniz MG et al (2015) Hsp27 (HSPB1) differential expression in normal salivary glands and pleomorphic adenomas and association with an increased Bcl2/Bax ratio. Tumor Biol 36(1):213–217

Del Signore AG, Megwalu UC (2017) The rising incidence of major salivary gland cancer in the United States. Ear Nose Throat J 96(3):E13–E16

Dong C, Hemminki K (2001) Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958–1996: a search for common mechanisms. Br J Cancer 85(7):997–1005

Ellis H (2012) Anatomy of the salivary glands. Surgery 30(11):569–572

Fu Y, Li J, Lee AS (2007) GRP78/BiP inhibits endoplasmic reticulum BIK and protects human breast cancer cells against estrogen starvation-induced apoptosis. Cancer Res 67(8):3734–3740

Galdirs TM, Kappler M, Reich W et al (2019) Current aspects of salivary gland tumors—a systematic review of the literature. GMS Interdiscip Plast Reconstr Surg DGPW 8:Doc12

Girdler R, Odell E, Putnam G (2016) Epidemiology and management of major salivary gland cancers. Public Health England, London

Ho K, Lin H, Ann DK et al (2011) An overview of the rare parotid gland cancer. Head Neck Oncol 3(1):40

Kessler AT, Bhatt AA (2018) Review of the major and minor salivary glands, part 1: anatomy, infectious, and inflammatory processes. J Clin Imaging Sci 8:47

Lo S, Di Palma S, Yusuf H et al (2005) Constitutive (HO-2) and inducible (HO-1) haem oxygenase in pleomorphic adenomas of the human parotid: an immunocytochemical study. J Laryngol Otol 119(3):179–183

Macario AJL, Conway de Macario E (2019) Chaperone proteins and chaperonopathies. Stress Physiol Biochem Pathol 3:135–152

Macario AJL, Conway de Macario E, Cappello F (2013) The chaperonopathies: diseases with defective molecular chaperones. Springer, Dordrecht

Mancuso TF, Brennan MJ (1970) Epidemiological considerations of cancer of the gallbladder, bile ducts and salivary glands in the rubber industry. J Occup Med 12(9):333–341

Ni M, Zhang Y, Lee AS (2011) Beyond the endoplasmic reticulum: atypical GRP78 in cell viability, signalling and therapeutic targeting. Biochem J 434(2):181–188

Parkin DM, Ferlay J, Curado MP et al (2010) Fifty years of cancer incidence: CI5 I-IX. Int J Cancer 127(12):2918–2927

Pfaffenbach KT, Lee AS (2011) The critical role of GRP78 in physiologic and pathologic stress. Curr Opin Cell Biol 23(2):150–156

Radoï L, Barul C, Menvielle G et al (2018) Risk factors for salivary gland cancers in France: results from a case-control study, the ICARE study. Oral Oncol 80:56–63

Rappa F, Sciume C, Lo Bello M, et al (2014) Comparative analysis of Hsp10 and Hsp90 expression in healthy mucosa and adenocarcinoma of the large bowel. Anticancer Res 34(8):4153–4159

Saku T, Hayashi Y, Takahara O et al (1997) Salivary gland tumors among atomic bomb survivors, 1950–1987. Cancer 79(8):1465–1475

Sangiorgi C, Vallese D, Gnemmi I et al (2017) HSP60 activity on human bronchial epithelial cells. Int J Immunopathol Pharmacol 30(4):333–340

Schneider AB, Favus MJ, Stachura ME et al (1977) Salivary gland neoplasms as a late consequence of head and neck irradiation. Ann Intern Med 87(2):160

Scriven P, Coulson S, Haines R et al (2009) Activation and clinical significance of the unfolded protein response in breast cancer. Br J Cancer 101(10):1692–1698

Seethala RR, Stenman G (2017) Update from the 4th edition of the world health organization classification of head and neck tumours: tumors of the salivary gland. Head Neck Pathol 11(1):55–67

Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67(1):7–30

Spitz MR, Sider JG, Newell GR (1990) Salivary gland cancer and risk of subsequent skin cancer. Head Neck 12(3):254–256

Tabatabai S, Tafti M, Rafiei B (2015) Primary malignant epithelial salivary gland tumors in an Iranian population: a retrospective study of 81 cases. J Oral Maxillofac Pathol 19(1):47–52

To VSH, Chan JYW, Tsang RKY et al (2012) Review of salivary gland neoplasms. ISRN Otolaryngol. https://doi.org/10.5402/2012/872982

Trenkić Božinović M, Krasić D, Katić V et al (2015) A retrospective review of 139 major and minor salivary gland tumors. Med Glas 12(1):73–78

Wang G, Gu X, Chen L et al (2013) Comparison of the expression of 5 heat shock proteins in benign and malignant salivary gland tumor tissues. Oncol Lett 5(4):1363–1369

Yamaguchi M, Abiko Y, Nishimura M et al (2004) An immunohistochemical study of the localization of inducible nitric oxide synthase (iNOS) and heat shock protein (HSP) in pleomorphic adenoma. Acta Histochem Cytochem 37(4):267–271

Zhang J, Jiang Y, Jia Z et al (2007) Association of elevated GRP78 expression with increased lymph node metastasis and poor prognosis in patients with gastric cancer. Clin Exp Metastasis 23(7–8):401–410