CANCER DIAGNOSIS & PROGNOSIS
4: 25-29 (2024) doi: 10.21873/cdp.10280

Review

PTEN Deregulation Mechanisms in Salivary Gland Carcinomas

VASILEIOS PAPANIKOLAOU[1], ARISTEIDIS CHRYSOVERGIS[1], MARIA ADAMOPOULOU[2*], DESPOINA SPYROPOULOU[3*], DIMITRIOS ROUKAS[4*], GEORGE PAPANASTASIOU[5*], SOFIANIKI MASTRONIKOLI[6], SOTIRIOS PAPOULIAKOS[7], LOUKAS MANAIOS[8], EVANGELOS TSIAMBAS[9], PAVLOS PANTOS[1], VASILEIOS RAGOS[5], PANAGOTIS FOTIADES[10], DIMITRIOS PESCHOS[11], NICHOLAS MASTRONIKOLIS[12] and EFTHYMIOS KYRODIMOS[1]

[1]*First Department of Otolaryngology, Hippocration Hospital, University of Athens, Athens, Greece;*
[2]*Biomedical Sciences Program, Department of Science and Mathematics, Deree American College, Athens, Greece;*
[3]*Department of Radiation Oncology, Medical School, University of Patras, Patras, Greece;*
[4]*Department of Psychiatry, 417 Veterans Army Hospital (NIMTS), Athens, Greece;*
[5]*Department of Maxillofacial Surgery, Medical School, University of Ioannina, Ioannina, Greece;*
[6]*Brighton and Sussex Medical School, Brighton, U.K.;*
[7]*Department of Otolaryngology, Gennimatas GNA Hospital, Athens, Greece;*
[8]*Department of Surgery, BIOCLINIC, Athens, Greece;*
[9]*Department of Cytology, 417 Veterans Army Hospital (NIMTS), Athens, Greece;*
[10]*Department of Surgery, 424 General Army Hospital, Thessaloniki, Greece;*
[11]*Department of Physiology, Medical School, University of Ioannina, Ioannina, Greece;*
[12]*Department of Otolaryngology, Medical School, University of Patras, Patras, Greece*

Abstract. *Among the tumour suppressor genes that affect critically cell functions and homeostasis, phosphatase and tensin homolog deleted in chromosome 10 (PTEN- gene locus: 10q21) regulates the PI3K/Akt/mTOR signalling pathway. PTEN is deleted, mutated or epigenetically hypermethylated in a variety of human solid malignancies. Salivary gland carcinomas (SGCs) belong to the head and neck carcinomas (HNCs) super category of solid malignancies. Histo-pathologically, they demonstrate a significant diversity due to a variety of distinct and mixed subtypes. Genetically, they are characterized by a broad spectrum of gene and chromosomal imbalances. Referring specifically to suppressor genes, PTEN deregulation plays a critical role in signaling transduction in the corresponding SGC pre- and malignant epithelia modifying the response rates to potential targeted therapeutic strategies. In the current review, we explored the role of PTEN deregulation mechanisms that are involved in the onset and progression of SGCs.*

Concerning the carcinogenic process in normal epithelia, there are two main categories of genes that critically enhance their neoplastic and malignant transformation (1-3). Over activation of oncogenes –such as RAS family members- combined with silencing of tumor suppressor genes negatively influence the cell cycle rhythm and a significant spectrum of signal transduction pathways in solid malignances of different histogenetic origin (4-6). Among suppressor genes, tumor phosphoprotein 53 (*TP53*, gene locus: 17p13) and phosphatase and tensin homolog deleted in chromosome 10 (*PTEN*-gene locus: 10q21) control crucial molecular pathways (7, 8). They are involved in apoptosis, cell arrest, DNA base repair, signalling transduction down-regulation, and generally in genome stability (9, 10). Specifically, *PTEN* encodes for a lipid phosphatase that

*These Authors contributed equally to this study.

Correspondence to: Evangelos Tsiambas, MD, MSc, Ph.D., Cytologist, 17 Patriarchou Grigoriou E' Street, Ag. Paraskevi 15341, Athens, Greece. E-mail: tsiambasecyto@yahoo.gr

Key Words: PTEN, suppressor gene, salivary, gland, mutation, review.

consists of two distinct domains: a C2 and a protein tyrosine phosphatase that provides its enzymatic activity (11). Normally, PTEN protein catalyses inositol dephosphorylation, whereas in neoplastic and cancerous cell this function is lost (12). This biochemical reaction is significant for the inhibition of Akt signalling pathway that regulates cell survival, growth, proliferation, migration, and tissue formation (13, 14). PTEN decreases the nuclear expression and localization of cyclin D1 cell cycle kinase preventing AKT over activation that promotes the cell cycle (15) Somatic mutations, deletions but also epigenetic silencing -due to hyper methylation of the *PTEN* gene promoter- have been detected in a variety of solid malignancies (16-18). For these reasons, *PTEN* functional silencing leads to an aberrant activation of the phosphoinositide 3-kinase/Phosphorylated protein kinase B/mammalian target of rapamycin (*PI3K/AKT/mTOR)* downstream genes that triggers an excessive signal transduction to the nucleus (19). Modern targeted therapeutic strategies based on *PTEN* enhancement combined with PI3K/AKT/MTOR protein pathway inhibition are under development and evaluation in solid malignancies (20-23). In the current review, we describe and analyze *PTEN* gene deregulation mechanisms in salivary gland carcinomas (SGCs) and explore their role in onset, progression, and biological behaviour.

SGCs: Histo-genetic Subtypes

Salivary gland epithelia are the histological substrates for the onset of a broad spectrum of solid malignancies. SGCs represent a subset of head and neck carcinoma (HNC) super family characterized by distinct histo-genetic profiles (24). World Health Organization (WHO) tumor classification identifies a variety of SGCs including predominantly mucoepidermoid (MEC), adenoid cystic (ADCC) and salivary duct (SDC) carcinomas (25). The first category (MEC) corresponds to well- and moderately-differentiated carcinomas affecting mainly the parotid glands (26). Additionally, ADCC is predominantly a well differentiated neoplasm and affects frequently all major glands. Interestingly, a sub-group of them demonstrates increased recurrence rates following surgical excision combined or not with a radiation-based therapeutic regimen (27). In contrast, SDCs represent high-grade malignancies characterized by local and distant metastases that appear as rapidly formed neck masses (28) Besides the abovementioned main SGC histotypes, there are also other less frequently observed including clear-cell carcinoma (CCC), basal cell adenocarcinoma (BCAD), acinic-cell carcinoma (ACC), cystadenocarcinoma (CADC), polymorphous adenocarcinoma (PADC), sebaceous adenocarcinoma (SADC), secretory carcinoma (CEC), mucinous adenocarcinoma (MADC), and sebaceous lymphadenocarcinoma (SLADC) (29). Furthermore, more ''exotic' and rare with increased biological aggressiveness carcinoma sub-types include epithelial–myoepithelial carcinoma (EMC), carcinoma ex pleomorphic adenoma (CexPAD), intra-ductal carcinoma (INDC), carcinosarcoma (CSC), squamous cell carcinoma (SCC), anaplastic small cell carcinoma (ASCC), and finally undifferentiated carcinomas (UNC) (30).

Differences have been reported, regarding gross chromosomal instability (CI) as aneuploidy/polysomy/ monosomy and related gene imbalances between SGCs histo-variants (31, 32). ADCs demonstrate a tendency for translocations and gene gains in chromosomes X/ 6/8, whereas SDCs are characterized by point mutations and amplifications of chromosome 17 genes (33, 34). BCC cases cytogenetically demonstrate deletions of specific loci on chromosome 16 (35). In contrast, MECs are characterized by translocations and deletions affecting chromosomes 9/1115/19 (36). Furthermore, rare subtypes, such as CexPAD and PADC are characterized by translocations and amplifications on chromosomes 8/12 and chromosomes X/1/2/14/19, respectively (34, 37). Similarly, gene amplifications and translocations on chromosomes 12/15/22 have been detected in CCCs and SECs (38).

PTEN Alterations in SGCs

PTEN suppressor gene silencing -due to mutations predominantly or deletion- leads to reduction of the corresponding protein expression levels in SDCs. Moreover, these genetic events combined with activation of specific oncogenes is responsible for the biological aggressiveness of the malignancy (39). According to a massive parallel sequencing gene analysis (MSK-IMPACT), a subset of examined SDCs demonstrated PTEN point mutations combined or not with mutated or amplified oncogenes including *ERBB2, PIK3CA, HRAS, ALK,* and *BRAF* (40). Interestingly, the combination of *PTEN* mutations and a novel HNRNPH3-ALK rearrangement -the ALK G1202R- was associated with increased resistance to targeted therapeutic regimens in the corresponding SDC and ex pleomorphic adenoma cases. Similarly, a study based on protein analysis by immunohistochemistry revealed loss of PTEN expression combined with HER2/neu over expression in a subset of SDCs (41).

Furthermore, the researchers suggested that high-mobility group AT-hook 2 (HMGA2) and PTEN should be considered potential targets for applying specific therapeutic strategies in SDCs. In another study, the researchers detected different PTEN/HER2/PI3KC/p AKT co-expression patterns in a series of SGCs that modify their biological behaviour (42). Analyzing the same molecules, another study group identified reduced PTEN protein expression, specifically in poorly differentiated solid SACCs (43). They also reported a combination of mTOR over activation and PTEN loss associated with an increased metastatic potential. According

to another study, combined PIK3CA mutations and PTEN deficiency are responsible for an aggressive SDC phenotype but also targets for specific chemotherapeutic regimens (44). Additionally, *PTEN* silencing leads to an excessive production of the WD repeat containing protein 66 (WDR66), which is involved in the onset and progression of the epithelial mesenchymal transition (EMT). Loss of PTEN functional activity is indirectly responsible for cancer cell proliferation and metastatic invasion (45).

Besides the main SGC histotypes, *PTEN* gene deregulation affects also rare and some "exotic'' SGCs variants. A next generation sequencing analysis in a series of aggressive salivary high-grade neuroendocrine carcinomas showed a co-downregulation of PTEN and retinoblastoma 1 (RB1) suppressor genes combined with overexpression of components of the PI3KCA/AKT/mTOR pathway (46). Furthermore, another genetic analysis in a series of apocrine SDCs revealed some cases characterized by PTEN mutation and others with deletion (47). Concerning another rare neoplasm, the murine salivary gland tumour (SGT), a study group detected a Smad and PTEN genes co-deletion that enhances its aggressiveness (48). Additionally, the combination of PTEN loss of expression due to mutations and the AKT/m TOR overactivation has been also reported in salivary gland secretory carcinoma (SSGC) (49). Similarly, PTEN mutations/deletions characterize a subset of the Carcinoma ex pleomorphic adenoma (CXPA). Additionally, hyalinising clear cell carcinoma (HCCC) subtype demonstrate similar genetic signatures (50, 51). In conjunction, another genetic analysis in secretory myoepithelial carcinomas (SMCA) - a very rare, signet ring-like mucinous carcinoma with a myoepithelial component – revealed very specific and unique PTEN mutation and splicing variant (c.655C>T p. Q219*, and c.1026+1G>A p. K342, respectively) (52). Similarly, a unique PTEN frameshift deletion (p. G36Dfs*18) has been detected in salivary gland intraductal papillary mucinous neoplasm (SG IPMN), a rare variant of SGC (53). Additionally, another ''exotic'' variant of SDC, the salivary duct carcinoma with rhabdoid transformation harbors combinations of specific mutations in *TP53* and *AKT* (54).

In conclusion, PTEN suppressor gene silencing plays a critical role in SGCs by enhancing signal transduction to the nucleus. Mechanisms of this deregulation include different point mutations and deletions of this specific gene locus that demonstrate in different SGC histo-types (55). PTEN silencing enhances PI3K/AKT/mTOR overactivation in pre- and malignant salivary gland epithelia. Additionally, PTEN deficiency modifies the response rates to potential targeted therapeutic strategies in SGCs that are based on specific genetic signatures detected by novel multi-gene molecular analyses (56, 57). In addition to *PTEN* down-regulation, differences among SGC histotypes are demonstrated by altered expression of factor-kappa B (NKkB1/p65), c-Jun N-terminal kinase (JNK1), growth arrest, and DNA damage (58). Finally, *PTEN* mutations are frequently combined with *PIK3CA* mutations, which also include a novel transforming growth factor (TFG)-PIK3CA fusion mechanism in borderline, neoplastic-like entities, such as sclerosing polycystic adenoma (59).

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

ET, AC, and VP: Design of the study and article writing; DS, DP, VR, NM, and EK: academic advisors; PF, AA, SP, DR, GP, LM, MA, and SM: collection and management of references and published data. All Authors read and approved the final article.

References

1 Stratton MR, Campbell PJ, Futreal PA: The cancer genome. Nature 458(7239): 719-724, 2009. DOI: 10.1038/nature07943

2 Albertson DG, Collins C, McCormick F, Gray JW: Chromosome aberrations in solid tumors. Nat Genet 34(4): 369-376, 2003. DOI: 10.1038/ng1215

3 Hanahan D, Weinberg RA: Hallmarks of cancer: The next generation. Cell 144(5): 646-674, 2011. DOI: 10.1016/j.cell.2011.02.013

4 Takase Y, Naito Y, Kawahara A, Okabe Y, Sadashima E, Abe H, Akiba J: KRAS mutation analysis using cell-free DNA of pancreatic cancer. Anticancer Res 43(6): 2683-2690, 2023. DOI: 10.21873/anticanres.16434

5 Papanikolaou V, Chrysovergis A, Mastronikolis S, Tsiambas E, Ragos V, Peschos D, Spyropoulou D, Pantos P, Niotis A, Mastronikolis N, Kyrodimos E: Impact of K-Ras over-expression in laryngeal squamous cell carcinoma. In Vivo 35(3): 1611-1615, 2021. DOI: 10.21873/invivo.12418

6 Asako K, Hayama T, Hashiguchi Y, Miyata T, Fukushima Y, Shimada R, Kaneko K, Nozawa K, Matsuda K, Fukagawa T: Prognostic value of KRAS Exon-specific mutations in patients with colorectal cancer. Anticancer Res 43(4): 1563-1568, 2023. DOI: 10.21873/anticanres.16306

7 Yang X, Jing D, Liu L, Shen Z, Ju J, Ma C, Sun M: Downregulation of p53 promotes in vitro perineural invasive activity of human salivary adenoid cystic carcinoma cells through epithelial-mesenchymal transition-like changes. Oncol Rep 33(4): 1650-1656, 2015. DOI: 10.3892/or.2015.3750

8 Hou CX, Sun NN, Han W, Meng Y, Wang CX, Zhu QH, Tang YT, Ye JH: Exosomal microRNA-23b-3p promotes tumor angiogenesis and metastasis by targeting PTEN in salivary adenoid cystic carcinoma. Carcinogenesis 43(7): 682-692, 2022. DOI: 10.1093/carcin/bgac033

9 Purvis JE, Karhohs KW, Mock C, Batchelor E, Loewer A, Lahav G: p53 dynamics control cell fate. Science 336(6087): 1440-1444, 2012. DOI: 10.1126/science.1218351

10 Mutter GL: Pten, a protean tumor suppressor. Am J Pathol 158(6): 1895-1898, 2001. DOI: 10.1016/S0002-9440(10)64656-1

11 Almalki WH: LncRNAs and PTEN/PI3K signaling: A symphony of regulation in cancer biology. Pathol Res Pract 249: 154764, 2023. DOI: 10.1016/j.prp.2023.154764
12 Liu J, Pan Y, Liu Y, Wei W, Hu X, Xin W, Chen N: The regulation of PTEN: Novel insights into functions as cancer biomarkers and therapeutic targets. J Cell Physiol 238(8): 1693-1715, 2023. DOI: 10.1002/jcp.31053
13 Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, Eng H, Nair MG, Makvandi P, Geoerger B, Kulke MH, Baird RD, Prabhu JS, Carbone D, Pecoraro C, Teh DBL, Sethi G, Cavalieri V, Lin KH, Javidi-Sharifi NR, Toska E, Davids MS, Brown JR, Diana P, Stebbing J, Fruman DA, Kumar AP: PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol Cancer 22(1): 138, 2023. DOI: 10.1186/s12943-023-01827-6
14 Manning BD, Cantley LC: AKT/PKB signaling: navigating downstream. Cell 129(7): 1261-1274, 2007. DOI: 10.1016/j.cell.2007.06.009
15 Hoxhaj G, Manning BD: The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. Nat Rev Cancer 20(2): 74-88, 2020. DOI: 10.1038/s41568-019-0216-7
16 Rodón J, Funchain P, Laetsch TW, Arkenau HT, Hervieu A, Singer CF, Murciano-Goroff YR, Chawla SP, Anthony K, Yamamiya I, Liu M, Halim AB, Benhadji KA, Takahashi O, Delaloge S: A phase II study of TAS-117 in patients with advanced solid tumors harboring germline PTEN-inactivating mutations. Future Oncol 18(30): 3377-3387, 2022. DOI: 10.2217/fon-2022-0305
17 Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X: Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer 18(1): 26, 2019. DOI: 10.1186/s12943-019-0954-x
18 Asati V, Mahapatra DK, Bharti SK: PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways inhibitors as anticancer agents: Structural and pharmacological perspectives. Eur J Med Chem 109: 314-341, 2016. DOI: 10.1016/j.ejmech.2016.01.012
19 Lee YR, Chen M, Pandolfi PP: The functions and regulation of the PTEN tumour suppressor: new modes and prospects. Nat Rev Mol Cell Biol 19(9): 547-562, 2018. DOI: 10.1038/s41580-018-0015-0
20 Yehia L, Ngeow J, Eng C: PTEN-opathies: from biological insights to evidence-based precision medicine. J Clin Invest 129(2): 452-464, 2019. DOI: 10.1172/JCI121277
21 Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C: Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 18(2): 400-407, 2012. DOI: 10.1158/1078-0432.CCR-11-2283
22 Xing Y, Lin NU, Maurer MA, Chen H, Mahvash A, Sahin A, Akcakanat A, Li Y, Abramson V, Litton J, Chavez-MacGregor M, Valero V, Piha-Paul SA, Hong D, Do KA, Tarco E, Riall D, Eterovic AK, Wulf GM, Cantley LC, Mills GB, Doyle LA, Winer E, Hortobagyi GN, Gonzalez-Angulo AM, Meric-Bernstam F: Phase II trial of AKT inhibitor MK-2206 in patients with advanced breast cancer who have tumors with PIK3CA or AKT mutations, and/or PTEN loss/PTEN mutation. Breast Cancer Res 21(1): 78, 2019. DOI: 10.1186/s13058-019-1154-8
23 Nagata Y, Lan K, Zhou X, Tan M, Esteva FJ, Sahin AA, Klos KS, Li P, Monia BP, Nguyen NT, Hortobagyi GN, Hung M, Yu D: PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell 6(2): 117-127, 2004. DOI: 10.1016/j.ccr.2004.06.022
24 Seethala RR, Stenman G: 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, 2017. DOI: 10.1007/s12105-017-0795-0
25 Ohshima H, Mishima K: Oral biosciences: The annual review 2022. J Oral Biosci 65(1): 1-12, 2023. DOI: 10.1016/j.job.2023.01.008
26 Arora S: Molecular genetics of head and neck cancer (Review). Mol Med Rep 6(1):19-22, 2012. DOI: 10.3892/mmr.2012.889
27 Skálová A, Hyrcza MD, Leivo I: Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands. Head Neck Pathol 16(1): 40-53, 2022. DOI: 10.1007/s12105-022-01420-1
28 Fukumura M, Ishibashi K, Nakaguro M, Nagao T, Saida K, Urano M, Tanigawa M, Hirai H, Yagyuu T, Kikuchi K, Yada N, Sugita Y, Miyabe M, Hasegawa S, Goto M, Yamamoto H, Ohuchi T, Kusafuka K, Ogawa I, Suzuki H, Notohara K, Shimoda M, Tada Y, Kirita T, Takata T, Morinaga S, Maeda H, Warnakulasuriya S, Miyabe S, Nagao T: Salivary gland polymorphous adenocarcinoma: Clinicopathological features and gene alterations in 36 Japanese patients. J Oral Pathol Med 51(8): 710-720, 2022. DOI: 10.1111/jop.13336
29 Syrnioti G, Syrnioti A, Abdullah A, Lui X, Mendoza E: Myoepithelial carcinoma ex pleomorphic adenoma of the submandibular gland: a case report. Cureus 15(3): e35722, 2023. DOI: 10.7759/cureus.35722
30 Nishida H, Kusaba T, Kawamura K, Oyama Y, Daa T: Histopathological aspects of the prognostic factors for salivary gland cancers. Cancers (Basel) 15(4): 1236, 2023. DOI: 10.3390/cancers15041236
31 Hamamoto Y, Harada H, Suzuki M, Fujii T, Nakatsuka SI: Salivary duct carcinoma of the parotid gland originating from an epithelial-myoepithelial carcinoma: report of a rare case. Head Neck Pathol 14(1): 283-289, 2020. DOI: 10.1007/s12105-019-01034-0
32 Kaur K, Mehta S, Vanik S, Trivedi P, Banerjee N, Dhar H, Datta S, Karanjai S: The evolving role of molecular pathology in the diagnosis of salivary gland tumours with potential pitfalls. Eur Arch Otorhinolaryngol 279(8): 3769-3783, 2022. DOI: 10.1007/s00405-022-07326-6
33 Gutschenritter T, Machiorlatti M, Vesely S, Ahmad B, Razaq W and Razaq M: Outcomes and prognostic factors of resected salivary gland malignancies: Examining a single institution's 12-year experience. Anticancer Res 37(9): 5019-5025, 2017. DOI: 10.21873/anticanres.11916
34 Sun L, Petrone JS, McNulty SN, Evenson MJ, Zhu X, Robinson JA, Chernock RD, Duncavage EJ, Pfeifer JD: Comparison of gene fusion detection methods in salivary gland tumors. Hum Pathol 123: 1-10, 2022. DOI: 10.1016/j.humpath.2022.02.002
35 Perissinotti AJ, Lee Pierce M, Pace MB, El-Naggar A, Kies MS, Kupferman M: The role of trastuzumab in the management of salivary ductal carcinomas. Anticancer Res 33(6): 2587-2591, 2013.
36 Chen Y, Li G, Jiang W, Nie RC, Deng H, Chen Y, Li H, Chen Y: Prognostic risk factor of major salivary gland carcinomas and survival prediction model based on random survival forests. Cancer Med 12(9): 10899-10907, 2023. DOI: 10.1002/cam4.5801
37 Bubola J, MacMillan CM, Demicco EG, Chami RA, Chung CT, Leong I, Marrano P, Onkal Z, Swanson D, Veremis BM, Weinreb

I, Zhang L, Antonescu CR, Dickson BC: Targeted RNA sequencing in the routine clinical detection of fusion genes in salivary gland tumors. Genes Chromosomes Cancer 60(10): 695-708, 2021. DOI: 10.1002/gcc.22979

38 Lee Y, Huang W, Hsieh M: CTNNB1 mutations in basal cell adenoma of the salivary gland. J Formos Med Assoc 117(10): 894-901, 2018. DOI: 10.1016/j.jfma.2017.11.011

39 Nakaguro M, Tada Y, Faquin WC, Sadow PM, Wirth LJ, Nagao T: Salivary duct carcinoma: Updates in histology, cytology, molecular biology, and treatment. Cancer Cytopathol 128(10): 693-703, 2020. DOI: 10.1002/cncy.22288

40 Dogan S, Ng CKY, Xu B, Kumar R, Wang L, Edelweiss M, Scott SN, Zehir A, Drilon A, Morris LGT, Lee NY, Antonescu CR, Ho AL, Katabi N, Berger MF, Reis-Filho JS: The repertoire of genetic alterations in salivary duct carcinoma including a novel HNRNPH3-ALK rearrangement. Hum Pathol 88: 66-77, 2019. DOI: 10.1016/j.humpath.2019.03.004

41 Liang L, Williams MD, Bell D: Expression of PTEN, androgen receptor, HER2/neu, cytokeratin 5/6, estrogen receptor-beta, HMGA2, and PLAG1 in salivary duct carcinoma. Head Neck Pathol 13(4): 529-534, 2019. DOI: 10.1007/s12105-018-0984-5

42 Saintigny P, Mitani Y, Pytynia KB, Ferrarotto R, Roberts DB, Weber RS, Kies MS, Maity SN, Lin SH, El-Naggar AK: Frequent PTEN loss and differential HER2/PI3K signaling pathway alterations in salivary duct carcinoma: Implications for targeted therapy. Cancer 124(18): 3693-3705, 2018. DOI: 10.1002/cncr.31600

43 Liu H, Du L, Wang R, Wei C, Liu B, Zhu L, Liu P, Liu Q, Li J, Lu SL, Xiao J: High frequency of loss of PTEN expression in human solid salivary adenoid cystic carcinoma and its implication for targeted therapy. Oncotarget 6(13): 11477-11491, 2015. DOI: 10.18632/oncotarget.3411

44 Griffith CC, Seethala RR, Luvison A, Miller M, Chiosea SI: PIK3CA mutations and PTEN loss in salivary duct carcinomas. Am J Surg Pathol 37(8): 1201-1207, 2013. DOI: 10.1097/PAS.0b013e3182880d5a

45 Cao Y, Liu H, Xia SL, Zhang X, Bai H, Yang Q, Li J, Gao L, Jin F, Wei MJ, Lu SL, Xiao J: PTEN downregulates WD repeat containing protein 66 in salivary adenoid cystic carcinoma. Oncol Rep 41(3): 1827-1836, 2019. DOI: 10.3892/or.2018.6931

46 Goyal B, Duncavage EJ, Martinez D, Lewis JS Jr, Chernock RD: Next-generation sequencing of salivary high-grade neuroendocrine carcinomas identifies alterations in RB1 and the mTOR pathway. Exp Mol Pathol 97(3): 572-578, 2014. DOI: 10.1016/j.yexmp.2014.10.011

47 Chiosea SI, Williams L, Griffith CC, Thompson LD, Weinreb I, Bauman JE, Luvison A, Roy S, Seethala RR, Nikiforova MN: Molecular characterization of apocrine salivary duct carcinoma. Am J Surg Pathol 39(6): 744-752, 2015. DOI: 10.1097/PAS.0000000000000410

48 Cao Y, Liu H, Gao L, Lu L, Du L, Bai H, Li J, Said S, Wang XJ, Song J, Serkova N, Wei M, Xiao J, Lu SL: Cooperation between Pten and Smad4 in murine salivary gland tumor formation and progression. Neoplasia 20(8): 764-774, 2018. DOI: 10.1016/j.neo.2018.05.009

49 Custódio M, Sedassari BT, Altemani A, Rodrigues MFSD, Nunes FD, de Sousa SCOM: Expression of upstream and downstream targets of mTOR pathway in seven cases of secretory carcinoma of salivary gland origin. Eur Arch Otorhinolaryngol 278(1): 279-283, 2021. DOI: 10.1007/s00405-020-06146-w

50 Key S, Chia C, Hasan Z, Sundaresan P, Riffat F, Dwivedi RC: Molecular factors in carcinoma ex pleomorphic adenoma: systematic review and meta-analysis. Laryngoscope, 2023. DOI: 10.1002/lary.30993

51 Kobayashi K, Kawazu M, Yoshimoto S, Ueno T, Omura G, Saito Y, Ando M, Ryo E, Sakyo A, Yoshida A, Yatabe Y, Mano H, Mori T: Genome doubling shapes high-grade transformation and novel EWSR1::LARP4 fusion shows SOX10 immunostaining in hyalinizing clear cell carcinoma of salivary gland. Lab Invest 103(10): 100213, 2023. DOI: 10.1016/j.labinv.2023.100213

52 Patel S, Wald AI, Bastaki JM, Chiosea SI, Singhi AD, Seethala RR: NKX3.1 Expression and molecular characterization of secretory myoepithelial carcinoma (SMCA): Advancing the case for a salivary mucous acinar phenotype. Head Neck Pathol 17(2): 467-478, 2023. DOI: 10.1007/s12105-023-01524-2

53 Nakaguro M, Sadow PM, Hu R, Hattori H, Kuwabara K, Tsuzuki T, Urano M, Nagao T, Faquin WC: NKX3.1 Expression in salivary gland "intraductal" papillary mucinous neoplasm: a low-grade subtype of salivary gland mucinous adenocarcinoma. Head Neck Pathol 16(4): 1114-1123, 2022. DOI: 10.1007/s12105-022-01471-4

54 Rooper LM, Gagan J, Bishop JA: Targeted molecular profiling of salivary duct carcinoma with rhabdoid features highlights parallels to other apocrine and discohesive neoplasms: which phenotype should drive classification? Head Neck Pathol 16(4): 1063-1072, 2022. DOI: 10.1007/s12105-022-01464-3

55 da Silva FJ, Carvalho de Azevedo J Jr, Ralph ACL, Pinheiro JJV, Freitas VM, Calcagno DQ: Salivary glands adenoid cystic carcinoma: a molecular profile update and potential implications. Front Oncol 13: 1191218, 2023. DOI: 10.3389/fonc.2023.1191218

56 Skálová A, Stenman G, Simpson RHW, Hellquist H, Slouka D, Svoboda T, Bishop JA, Hunt JL, Nibu KI, Rinaldo A, Vander Poorten V, Devaney KO, Steiner P, Ferlito A: The role of molecular testing in the differential diagnosis of salivary gland carcinomas. Am J Surg Pathol 42(2): e11-e27, 2018. DOI: 10.1097/PAS.0000000000000980

57 Li J, Mitani Y, Rao PH, Perlaky L, Liu B, Weber RS, El-Naggar AK: Establishment and genomic characterization of primary salivary duct carcinoma cell line. Oral Oncol 69: 108-114, 2017. DOI: 10.1016/j.oraloncology.2017.04.007

58 Gobel G, Szanyi I, Révész P, Bauer M, Gerlinger I, Németh Á, Ember I, Gocze K, Gombos K: Expression of NFkB1, GADD45A and JNK1 in salivary gland carcinomas of different histotypes. Cancer Genomics Proteomics 10(2): 81-87, 2013.

59 Hernandez-Prera JC, Saeed-Vafa D, Heidarian A, Gewandter K, Otto K, Wenig BM: Sclerosing polycystic adenoma: Conclusive clinical and molecular evidence of its neoplastic nature. Head Neck Pathol 16(2): 416-426, 2022. DOI: 10.1007/s12105-021-01374-w

Received October 4, 2023
Revised November 12, 2023
Accepted November 13, 2023