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Pathogenesis and Molecular-Genetic Aspects of Salivary Gland Tumors

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Annotation: This article analyzes the molecular-genetic mechanisms underlying the development of salivary gland tumors. Key genetic mutations (PLAG1, HMGA2, CTNNB1) and their impact on tumor growth are examined. The role of dysregulated signaling pathways (Wnt/β-catenin, PI3K/AKT/mTOR, NF-kB) in carcinogenesis is highlighted. Particular attention is given to the expression of molecular markers (CK7, p40, p63, SOX10, S-100) and their diagnostic significance. The influence of chronic inflammation and pro-inflammatory cytokines (IL-6, TNF-α) on tumor progression is discussed. This review underscores the need for further research to develop new diagnostic and therapeutic strategies aimed at identifying molecular targets and improving approaches to the treatment of salivary gland tumors.

Keywords: salivary gland tumors, molecular-genetic mechanisms, PLAG1, HMGA2, CTNNB1, signaling pathways, Wnt/β-catenin, PI3K/AKT/mTOR, NF-kB, molecular markers, CK7, p40, p63, SOX10, S-100, inflammation, IL-6, TNF-α.

Introduction. Salivary gland tumors are a heterogeneous group of neoplasms characterized by significant morphological and biological diversity. Despite their relatively rare occurrence compared to tumors of other localizations, these neoplasms represent a serious clinical problem. This is due to their potential malignancy, tendency to infiltrative growth and recurrence, as well as difficulties in differential diagnosis [1,2]. In this regard, the study of tumor formation mechanisms, including genetic and molecular aspects, is of particular relevance.

Classification of salivary gland tumors includes both benign and malignant neoplasms. Among benign tumors, the most common is pleomorphic adenoma, while among malignant tumors, the most common are mucoepidermoid cancer, adenoid cystic cancer, and acinar cell carcinoma. The incidence of malignant tumors varies significantly depending on the specific location and type of gland. The importance of studying these neoplasms is due to their aggressive clinical course, the possibility of metastasis, and limited therapeutic options, especially in the case of late diagnosis [3,4].

Modern research in the field of molecular oncology allows us to study in more depth the mechanisms of salivary gland tumor development, including genetic mutations, dysregulation of signaling pathways, and expression of molecular markers. This review article discusses the key molecular genetic aspects of tumorigenesis, including the role of PLAG1, HMGA2, and CTNNB1 gene mutations, as well as the influence of the Wnt/β-catenin, PI3K/AKT/mTOR, and NF-kB signaling pathways. In addition, special attention is paid to the expression of diagnostically significant markers (CK7, p40, p63, SOX10, S-100) and the role of inflammatory factors (IL-6, TNF-α) in tumor progression. Analysis of these mechanisms not only contributes to a deeper understanding of pathogenesis, but also opens up new perspectives for the development of diagnostic and therapeutic strategies.

Genetic mechanisms of tumor formation

The development of salivary gland tumors is a complex process based on various molecular genetic disorders. Genetic mutations play a key role in the initiation and progression of neoplasms, leading to uncontrolled cell proliferation, changes in their differentiation and ability to invade. Recent studies have identified a number of specific genes, mutations and dysregulation of which are associated with tumor growth in the salivary glands. Among them, the most important are PLAG1, HMGA2 and

CTNNB1, which are involved in the regulation of the cell cycle, differentiation and intercellular interactions [5,6].

One of the key oncogenes involved in tumorigenesis is PLAG1 (pleomorphic adenoma gene 1). This transcription factor plays an important role in regulating the expression of various genes associated with cell growth and proliferation. Mutations or translocations leading to hyperexpression of PLAG1 are often detected in pleomorphic adenomas of the salivary glands. It has been established that increased activity of this gene contributes to the disruption of normal mechanisms of cell division control, which ultimately leads to tumor transformation [7,8].

Another important gene associated with tumor growth is HMGA2 (high-mobility group AT-hook 2). Normally, HMGA2 is involved in embryonic development, regulating the expression of genes responsible for cellular plasticity. However, under conditions of tumor transformation, its abnormal expression promotes increased cell proliferation, suppression of apoptosis, and increased migration activity. Dysregulation of HMGA2 has been shown to be associated with aggressive forms of salivary gland tumors, making it an important molecular marker of tumor progression [8,9]. CTNNB1 (catenin beta-1), encoding β-catenin, a protein involved in the formation of adhesive contacts and activation of the Wnt/β-catenin signaling pathway, plays an equally significant role in the pathogenesis of salivary gland tumors. Disruptions in the functioning of CTNNB1, including mutations leading to stabilization of β-catenin, contribute to excessive activation of this signaling pathway. As a result, the expression of proliferative genes increases, which leads to disruption of intercellular coordination and progression of the tumor process [10,11].

Dysregulation of signaling pathways in tumor growth

Tumor transformation of salivary gland cells is caused not only by genetic mutations, but also by disruption of key signaling pathways that regulate cell growth, differentiation, and apoptosis. Among the most significant pathways involved in carcinogenesis are Wnt/β-catenin, PI3K/AKT/mTOR, and NF-kB, which play a central role in maintaining the proliferative activity of tumor cells, their survival, and their ability to invade. Dysregulation of these signaling cascades contributes to the development of a malignant phenotype, making them promising targets for therapeutic intervention [12,13,14].

One of the most studied signaling mechanisms in tumor pathogenesis is the Wnt/β-catenin pathway, which regulates cell proliferation and differentiation. Normally, β-catenin, encoded by the CTNNB1 gene, is involved in intercellular contacts and signal transmission to the nucleus. However, during tumor transformation, mutations occur that lead to stabilization of β-catenin and its accumulation in the cytoplasm, which activates the transcription of genes responsible for cell growth and suppression of apoptosis. Hyperactivation of the Wnt/β-catenin pathway contributes to the formation of an aggressive phenotype of tumor cells and their resistance to traditional therapy [12,15]**.**

Another key signaling pathway that plays an important role in tumor growth is the PI3K/AKT/mTOR pathway. It is responsible for the regulation of cellular metabolism, angiogenesis, and tumor cell survival. Activation of this cascade occurs through phosphoinositide 3-kinase (PI3K), which triggers phosphorylation of the AKT protein, leading to activation of the target of rapamycin (mTOR). Dysregulation of this pathway is observed in malignant tumors of the salivary glands and leads to increased cell resistance to apoptosis, increased migratory activity, and metastatic potential. In addition, mutations in the PIK3CA and PTEN genes involved in the regulation of this pathway contribute to its hyperactivation and aggressive tumor growth [16,17]. Finally, the NF-kB signaling pathway, which is involved in the regulation of the inflammatory response and cell survival, plays an important role in the carcinogenesis of salivary gland tumors. Normally, this cascade is activated by the action of proinflammatory cytokines or stress, providing protective mechanisms for the cell. However, during tumor transformation, its chronic activation occurs, which leads to increased expression of genes responsible for angiogenesis, anti-apoptotic protection, and the development of an inflammatory tumor microenvironment. The relationship between chronic inflammation and malignant growth, mediated by NF-kB, emphasizes the importance of this pathway in the formation of the tumor microenvironment and cell resistance to therapy [18,19].

Expression of molecular markers of salivary gland tumors

Diagnostics of salivary gland tumors is a complex task due to their high morphological heterogeneity. In this regard, the study of molecular markers is of particular importance, the expression of which allows not only to differentiate various histological types of tumors, but also to clarify their origin, biological behavior and prognosis. Among the most significant markers used in immunohistochemical diagnostics are cytokeratins (CK7), transcription factors (p40, p63) and neural markers (SOX10, S-100), which play a key role in the characterization of tumor cells [20].

One of the most important markers of epithelial tumors of the salivary glands is CK7, a protein belonging to the cytokeratin family and involved in the formation of the cytoskeleton of epithelial cells. CK7 expression is characteristic of most adenocarcinomas, including mucoepidermoid carcinoma and adenoid cystic carcinoma, making it a valuable diagnostic tool in the study of neoplasia of this localization. In addition, this marker is used in the differential diagnosis between salivary gland tumors and neoplasms of other organs, which is especially important in identifying metastatic lesions [2,21].

In addition to cytokeratins, transcription factors p40 and p63, which are markers of cells of basal and myoepithelial origin, play an important role in the diagnosis of malignant tumors. p63, which belongs to the p53 family, is expressed in basal epithelial cells and is used to identify squamous cell and myoepithelial tumors. At the same time, p40, which is a truncated isoform of p63, has a high specificity for squamous cell tumors, which allows it to be used to differentiate mucoepidermoid cancer from other neoplasms [22,23]. In addition to epithelial markers, neural markers such as SOX10 and S-100, which allow the identification of tumors of myoepithelial and neurogenic origin, have significant diagnostic value. SOX10 is a transcription factor regulating neural crest cell development, and its expression is characteristic of pleomorphic adenoma, adenoid cystic carcinoma, and secretory salivary gland carcinoma. This marker has high sensitivity and specificity, which makes it an important diagnostic tool. In turn, S-100, a protein associated with cell differentiation and migration, is also widely used to confirm myoepithelial and schwannomatous differentiation of tumors [24,25,26].

The relationship between inflammatory processes and tumor progression

Chronic inflammation plays a significant role in carcinogenesis, contributing to the initiation, maintenance and progression of the tumor process. Long-term activation of inflammatory mechanisms is accompanied by the release of proinflammatory cytokines, reactive oxygen and nitrogen species, as well as remodeling of the extracellular matrix, which creates favorable conditions for cell malignancy. In the context of salivary gland tumors, inflammation not only stimulates the proliferation of malignant cells, but also affects their resistance to apoptosis, angiogenesis and invasive properties.

One of the key inflammatory mediators involved in tumor progression is interleukin-6 (IL-6). This cytokine plays a multifunctional role in the regulation of the immune response, cell proliferation and survival. Increased expression of IL-6 in salivary gland tumor tissue is associated with activation of the JAK/STAT3 signaling pathway, which leads to increased growth of malignant cells, suppression of their apoptosis and development of drug resistance. In addition, IL-6 promotes differentiation of tumor microenvironment fibroblasts into activated myofibroblasts, which maintain an aggressive tumor phenotype [27,28]. Another important proinflammatory cytokine involved in carcinogenesis is tumor necrosis factor alpha (TNF-α). Its main biological action is to modulate the inflammatory response and remodel the tumor microenvironment. High levels of TNF-α in salivary gland tumors promote activation of the NF-kB signaling pathway, which regulates the expression of genes responsible for cell survival, angiogenesis and immunosuppression. Moreover, TNF-α stimulates the expression of adhesion molecules and metalloproteinases, promoting invasive growth of tumor cells and their dissemination into surrounding tissues [29,30].

Conclusion

Salivary gland tumors are a heterogeneous group of neoplasms with different biological behavior and molecular genetic characteristics. Analysis of modern data indicates the important role of genetic

mutations, dysregulation of signaling pathways, expression of molecular markers and inflammatory processes in the development and progression of these tumors.

Study of genetic mechanisms of tumor formation allowed us to identify key genes, such as PLAG1, HMGA2 and CTNNB1, mutations and overexpression of which lead to impaired cell proliferation and differentiation. In turn, the imbalance of the Wnt/β-catenin, PI3K/AKT/mTOR and NF-kB signaling pathways plays a critical role in maintaining the malignant phenotype of tumor cells, promoting their growth, angiogenesis and resistance to apoptosis. Expression of molecular markers such as CK7, p40, p63, SOX10 and S-100 has additional diagnostic and prognostic value, allowing for more accurate differentiation of histological tumor subtypes and determination of their potential aggressiveness. Particular attention is drawn to the relationship between inflammatory processes and tumor progression, since proinflammatory cytokines IL-6 and TNF-α not only create a favorable microenvironment for tumor cells, but also promote their proliferation, angiogenesis and invasion.

List of references:

1. Santos D, Rodrigues-Fernandes ES, Speight CI, Khurram PM, Alsanie SA, Normando I, et al. Impact of tumor site on the prognosis of salivary gland neoplasms: A systematic review and meta-analysis. Critical reviews in oncology/hematology. 2021;162.
2. Egal ESA, Scarini JF, de Lima-Souza RA, Lavareze L, Fernandes PM, Emerick C, et al. Tumor microenvironment in salivary gland carcinomas: An orchestrated state of chaos. Oral Oncol [Internet]. 2022;127(105777):105777. Available from: http://dx.doi.org/10.1016/j.oraloncology.2022.105777
3. 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 [Internet]. 2022;16(1):40–53. Available from: http://dx.doi.org/10.1007/s12105-022-01420-1
4. Żurek M, Fus Ł, Niemczyk K, Rzepakowska A. Salivary gland pathologies: evolution in classification and association with unique genetic alterations. Eur Arch Otorhinolaryngol [Internet]. 2023;280(11):4739–50. Available from: http://dx.doi.org/10.1007/s00405-023-08110-w
5. Shi Z-D, Pang K, Wu Z-X, Dong Y, Hao L, Qin J-X, et al. Tumor cell plasticity in targeted therapy-induced resistance: mechanisms and new strategies. Signal Transduct Target Ther [Internet]. 2023;8(1):113. Available from: http://dx.doi.org/10.1038/s41392-023-01383-x
6. Toper MH, Sarioglu S. Molecular pathology of salivary gland neoplasms: Diagnostic, prognostic, and predictive perspective: Diagnostic, prognostic, and predictive perspective. Adv Anat Pathol [Internet]. 2021;28(2):81–93. Available from: http://dx.doi.org/10.1097/PAP.0000000000000291
7. Naik U, Amin SE, Elsayad M, Saluja K. Pleomorphic Adenoma with a Novel Gene Rearrangement-LINC01606:: PLAG1. Head and Neck Pathology. 2024;18.
8. Owosho AA, Adesina OM, Odujoko O, Akinyemi H, Komolafe A, Tadros S, et al. HMGA2 Immunoexpression is frequent in salivary gland pleomorphic adenoma: immunohistochemical and molecular analyses of PLAG1 and HMGA2 in 25 cases. Int J Clin Exp Pathol. 2022;15(2):63–71.
9. Broseghini E, Carosi F, Berti M, Compagno S, Ghelardini A, Fermi M, et al. Salivary gland cancers in the era of molecular analysis: The role of tissue and liquid biomarkers. Cancers (Basel) [Internet]. 2025;17(4). Available from: http://dx.doi.org/10.3390/cancers17040660
10. Swid MA, Li L, Drahnak EM, Idom H, Quinones W. Updated salivary gland immunohistochemistry: A review. Arch Pathol Lab Med [Internet]. 2023;147(12):1383–9. Available from: http://dx.doi.org/10.5858/arpa.2022-0461-RA
11. Pikul J, Rzepakowska A. Molecular landscape of salivary gland malignancies. What is already known? Contemp Oncol (Pozn) [Internet]. 2024;28(3):201–16. Available from: http://dx.doi.org/10.5114/wo.2024.144288

12. Song P, Gao Z, Bao Y, Chen L, Huang Y, Liu Y, et al. Wnt/β-catenin signaling pathway in carcinogenesis and cancer therapy. J Hematol Oncol [Internet]. 2024;17(1):46. Available from: http://dx.doi.org/10.1186/s13045-024-01563-4

13. Stefani C, Miricescu D, Stanescu-Spinu I-I, Nica RI, Greabu M, Totan AR, et al. Growth factors, PI3K/AKT/mTOR and MAPK signaling pathways in colorectal cancer pathogenesis: Where are we now? Int J Mol Sci [Internet]. 2021;22(19):10260. Available from: http://dx.doi.org/10.3390/ijms221910260

14. Moneva-Sakelarieva M, Kobakova Y, Konstantinov S, Momekov G, Ivanova S, Atanasova V, et al. The role of the transcription factor NF-kB in the pathogenesis of inflammation and carcinogenesis. Modulation capabilities. Pharmacia. 2025;72:1–13.

15. He K, Gan WJ. Wnt/β-catenin signaling pathway in the development and progression of colorectal cancer. Cancer Management and Research. 2023;435–48.

16. Ouedraogo SY, Zoure AA, Zeye MMJ, Kiendrebeogo TI, Zhou X, Sawadogo AY, et al. BRCA1, BRCA2, TP53, PIK3CA, PTEN and AKT1 genes mutations in Burkina Faso breast cancer patients: prevalence, spectrum and novel variant. Mol Genet Genomics [Internet]. 2022;297(5):1257–68. Available from: http://dx.doi.org/10.1007/s00438-022-01914-1

17. Panwar V, Singh A, Bhatt M, Tonk RK, Azizov S, Raza AS, et al. Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. Signal Transduct Target Ther [Internet]. 2023;8(1):375. Available from: http://dx.doi.org/10.1038/s41392-023-01608-z

18. De Mello Gomes ÁN, Oliveira KK, Marchi FA, Bettim BB, Germano JN, Gonçalves Filho J, et al. TGFβ signaling pathway in salivary gland tumors. Archives of Oral Biology. 2024;162.

19. Basset CA, Hajj Hussein I, Jurjus AR, Cappello F, Conway de Macario E, Macario AJL, et al. The chaperone Hsp90, a key player in salivary gland tumorigenesis. Applied Biosciences [Internet]. 2023;2(4):607–16. Available from: http://dx.doi.org/10.3390/applbiosci2040038

20. Nonaka T, Takei H. Immunohistochemical profile of polymorphous adenocarcinoma of minor salivary gland: A systematic review and meta-analysis. Head Neck Pathol [Internet]. 2022;16(4):980–90. Available from: http://dx.doi.org/10.1007/s12105-022-01453-6

21. Ruddle NH. Regulation, maintenance, and remodeling of high endothelial venules in homeostasis, inflammation, and cancer. Current Opinion in Physiology. 2023;36.

22. Sivakumar N, Narwal A, Pandiar D, Devi A, Anand R, Bansal D, et al. Diagnostic utility of p63/p40 in the histologic differentiation of salivary gland tumors: a systematic review. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2022;133:189–98.

23. Steurer S, Riemann C, Büscheck F, Luebke AM, Kluth M, Hube-Magg C, et al. P63 expression in human tumors and normal tissues: A tissue microarray study on 10,200 tumors. Biomark Res [Internet]. 2021;9(1):7. Available from: http://dx.doi.org/10.1186/s40364-021-00260-5

24. Gonzalez MF, Husain BH. Solitary fibrous tumour of the submandibular gland: Novel insights from clinical practice on a close mimicker of pleomorphic adenoma and a diagnostic challenge for the cytopathologist. Cytopathology [Internet]. 2021;32(2):261–5. Available from: http://dx.doi.org/10.1111/cyt.1293

25. Naso JR, Roden AC. Recent developments in the pathology of primary pulmonary salivary gland-type tumours. Histopathology. 2024;84(1):102–23.

26. Thompson LD. Immunohistology of Head and Neck. Diagnostic Immunohistochemistry E-Book: Diagnostic Immunohistochemistry E-Book. 2021;254.

27. Ismerim AB, de Oliveira Araújo IB, de Aquino Xavier FC, Rocha CAG, Macedo CL, Cangussu MCT, et al. Mast cells and proteins related to myofibroblast differentiation (PAR-2, IL-6, and

TGFβ1) in salivary cancers: A preliminary study: A preliminary study. Appl Immunohistochem Mol Morphol [Internet]. 2021;29(7):e57–67. Available from: http://dx.doi.org/10.1097/PAI.0000000000000924

28. Barrera MJ. Tofacitinib counteracts IL-6 overexpression induced by deficient autophagy: implications in Sjögren's syndrome //Rheumatology. - 2021. - T. 60. :1951–62.

29. Brierly G, Celentano A, Breik O, Moslemivayeghan E, Patini R, McCullough M, et al. Tumour necrosis factor alpha (TNF-α) and oral squamous cell carcinoma. Cancers (Basel) [Internet]. 2023;15(6). Available from: http://dx.doi.org/10.3390/cancers15061841