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BIOMARKERS OF ORAL SQUAMOUS CELL CARCINOMA: POTENTIAL DIAGNOSTIC AND PROGNOSTIC TOOLS

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Abstract

Oral squamous cell carcinoma (OSCC) is a prevalent malignant tumor, where early diagnosis and effective prognostic assessment are crucial for improving patient outcomes. In recent years, biomarkers have attracted significant attention in OSCC research, emerging as potential tools for diagnosis and prognosis. This review summarizes the latest advancements in the study of biomarkers associated with oral squamous cell carcinoma, including various types of biomarkers such as genes, proteins, and non-coding RNA, and evaluates their application value in early detection, treatment response assessment, and prognostic judgment. By conducting a comprehensive analysis of the existing literature, this paper aims to provide insights that can enhance clinical practice.

Keywords: Oral squamous cell carcinoma; Biomarkers; Early diagnosis; Prognostic assessment; Tumor biology

1. Introduction

Oral squamous cell carcinoma (OSCC) is a significant health concern worldwide, characterized by its high incidence and mortality rates. Epidemiological studies indicate that OSCC is one of the most prevalent forms of oral cancer, with varying incidence across different geographic regions. Factors such as tobacco use, alcohol consumption, and human papillomavirus (HPV) infection have been identified as major risk factors contributing to the development of OSCC. For instance, HPV-related lesions have been increasingly recognized as significant contributors to the pathogenesis of OSCC, particularly in younger populations (Betz, 2019). Furthermore, poor oral health, including periodontal disease and tooth loss, has been shown to correlate with an increased risk of OSCC, suggesting a complex interplay between oral hygiene and cancer development (Da Silva et al., 2024; Tasoulas et al., 2024).

Biomarkers, defined as biological molecules that indicate a physiological or pathological process, play a crucial role in oncology. They serve as indicators for disease progression, treatment response, and overall prognosis. In the context of OSCC, biomarkers can enhance our understanding of tumor biology and facilitate early detection, which is critical for improving patient outcomes. For example, the identification of specific genetic alterations and molecular signatures associated with OSCC can lead to the development of targeted therapies and personalized treatment plans (Bakker et al., 2023). The growing interest in precision medicine underscores the importance of biomarkers in tailoring therapeutic strategies to individual patient profiles, ultimately aiming to improve survival rates and quality of life for patients with OSCC (Tran et al., 2020).

The purpose of this review is to explore the epidemiology and clinical characteristics of OSCC, with a focus on the role of biomarkers in its diagnosis and treatment. By synthesizing current research findings, this review aims to highlight the significance of biomarkers in the clinical management of OSCC and discuss potential future directions for research in this area. Understanding the relationship between biomarkers and OSCC not only contributes to the existing body of knowledge but also has significant implications for enhancing patient care and treatment outcomes in this challenging disease landscape.

2. Genetic biomarkers for TSCC

2.1 TP53

The TP53 gene, often called the "guardian of the genome," is critical in regulating the cell cycle and maintaining genomic stability. Mutations in TP53 are one of the most common genetic alterations found in OSCC. These mutations can produce a dysfunctional p53 protein, which fails to execute its tumor-suppressive functions, thus promoting tumorigenesis. Studies have shown that TP53 mutations are associated with more aggressive disease and poorer prognosis in OSCC patients (J. H. Ji et al., 2022). Furthermore, the presence of TP53 mutations has been linked to specific clinical features, including advanced tumor stage and increased likelihood of metastasis (Romanovsky et al., 2023). Recent research utilizing whole-exome sequencing has identified novel mutations in the TP53 gene that affect the DNA damage repair and apoptosis pathways, underscoring the multifaceted role of TP53 in OSCC pathogenesis (F. Xie et al., 2022). Additionally, the heterogeneity of TP53 mutations within tumors suggests that different subclonal populations may exhibit varying responses to therapy, complicating treatment strategies (Tang & Chen, 2024). Overall, the TP53 mutation landscape in OSCC highlights its importance as a biomarker for prognosis and therapeutic targeting.

2.2 NOTCH1

The NOTCH gene is a highly conserved and evolutionarily ancient gene that is universally present in cells. On one hand, it plays a crucial role in the normal growth and development of mammals,

as well as in tissue homeostasis. On the other hand, it has also been reported to be inextricably linked to the occurrence and progression of many diseases, such as cancer (Artavanis-Tsakonas, 1988; Leong & Karsan, 2006). The role of the NOTCH signaling pathway in tumors is currently unclear. It plays different roles in various tumors, and even within the same tumor, it may simultaneously have both tumor-suppressing and oncogenic effects (Abby et al., 2023; Agrawal et al., 2011; Ellisen et al., 1991; Jafari et al., 2020; X. Jiao et al., 2012; Puente et al., 2011; Stransky et al., 2011; N. J. Wang et al., 2011; Weng et al., 2004; Yi et al., 2022).

NOTCH1 is the second most common mutated gene in whole-exome sequencing of HNSCC (Agrawal et al., 2011; Schmidl et al., 2022; Stransky et al., 2011). There is still considerable debate over the exact role of the NOTCH signaling pathway in oral squamous cell carcinoma. Some scholars have found that high expression of NOTCH can promote the proliferation, migration, and invasion of head and neck squamous cell carcinoma cells (Inamura et al., 2017; Weaver et al., 2016), and is closely related to tumor invasion, distant metastasis, and poor prognosis in patients (Morita et al., 2017; Tian et al., 2018). The combination of NOTCH signaling pathway inhibitors and EGFR inhibitors can inhibit the proliferation and migration of head and neck squamous cell carcinoma cells (Zheng et al., 2018). The expression of NOTCH promotes the cancer stem cell characteristics of head and neck squamous cell carcinoma (Lee et al., 2016). The NOTCH signaling pathway is associated with tumor immune escape in head and neck squamous cell carcinoma, and inhibiting the NOTCH signaling pathway can reduce immune-suppressive cells within the tumor (Mao et al., 2018). a pivotal role for ZMIZ1 as an oncogenic driver, possibly operating by activating the Notch1 signaling pathway, thereby facilitating TSCC invasion and migration. Yunqing Pang et al. found that ZMIZ1 plays a key role as an oncogenic driver, possibly by activating the Notch1 signaling pathway, thereby promoting the invasion and migration of tongue squamous cell carcinoma (Pang et al., 2024). Therefore, these scholars believe that NOTCH plays the role of an oncogene in head and neck squamous cell carcinoma. Conversely, some researchers have found that the activation of NOTCH1 in head and neck squamous cell carcinoma cells inhibits tumor cell proliferation, leading to cell cycle arrest and increased cellular senescence (J. Jiao et al., 2009; Pickering et al., 2013). NOTCH1 has a higher nonsense mutation rate in HNSCC, and PTC124 can rescue these nonsense mutations, inhibiting the proliferation of HNSCC cells (Wu et al., 2022). Disabling the NOTCH signaling pathway in transgenic mice promotes the growth of head and neck tumors (Nyman et al., 2018). By expressing or activating the estrogen receptor, the expression of NOTCH is elevated, thereby inhibiting the proliferation of squamous cell carcinoma (Brooks et al., 2014). Overexpression of NOTCH can also improve the survival rate of patients with head and neck squamous cell carcinoma (Kaka et al., 2017; Wirth et al., 2018). Wu-Chou et al. found that NOTCH1 mutations are very common in OSCC and are associated with a shortened overall survival in OSCC patients (Grilli et al., 2020; Wu-Chou et al., 2021). Therefore, these scholars believe that NOTCH1 plays the role of a tumor suppressor gene in head and neck squamous cell carcinoma.

2.3 P16INK4a

P16INK4a, a cyclin-dependent kinase inhibitor, plays a pivotal role in regulating the cell cycle by inhibiting cyclin D-CDK4/6 complexes, thereby promoting cellular senescence. In the context of OSCC, the expression levels of P16INK4a have been extensively studied due to its association with human papillomavirus (HPV) infection and its potential as a prognostic marker. Elevated expression of P16INK4a is often observed in HPV-positive OSCC patients, indicating a distinct biological behavior compared to HPV-negative cases (Kravets et al., 2023). The overexpression of P16INK4a has been correlated with improved clinical outcomes, suggesting its role as a favorable prognostic indicator in OSCC (Thin et al., 2022). Moreover, P16INK4a's expression has been utilized as a diagnostic marker to differentiate between HPV-related and non-HPV-related OSCC, which is crucial for tailoring treatment approaches (Hakeem

et al., 2020). However, the expression of P16INK4a can also be influenced by other factors, including genetic alterations and the tumor microenvironment, highlighting the need for further research to fully elucidate its role in OSCC pathogenesis.

2.4 Impact of HPV-Related Genes

The relationship between human papillomavirus (HPV) and oral squamous cell carcinoma has garnered significant attention in recent years, particularly concerning the oncogenic potential of HPV-related genes such as E6 and E7. HPV-positive OSCC is characterized by the integration of viral DNA into the host genome, leading to the expression of E6 and E7 proteins, which disrupt normal cell cycle regulation and promote cellular transformation. E6 protein binds to and promotes the degradation of the p53 tumor suppressor protein, while E7 protein inactivates the retinoblastoma protein (pRb), resulting in unregulated cell proliferation (Ma et al., 2020). Studies have indicated that HPV-positive OSCC patients tend to have better clinical outcomes compared to their HPV-negative counterparts, which may be attributed to the distinct biological behavior of HPV-associated tumors (Morand et al., 2022). Furthermore, the expression levels of HPV oncogenes have been linked to specific immune responses within the tumor microenvironment, suggesting that HPV status may influence therapeutic responses (Berglund et al., 2022). Understanding the molecular mechanisms by which HPV-related genes contribute to OSCC pathogenesis is essential for developing targeted therapies and improving patient outcomes.

3. Proteins biomarkers for TSCC

3.1 SOX

The SOX family of transcription factors plays a complex role in cancer, involving aspects such as tumor invasion, metastasis, proliferation, apoptosis, epithelial-mesenchymal transition (EMT), stemness, and drug resistance. The abnormal expression of SOX family members is closely related to the occurrence and development of cancer, with SOX2, SOX4, and SOX9 being the most studied members. They promote EMT and stemness of tumors by affecting signaling pathways such as Wnt/β-catenin and TGF-β, and are associated with tumor prognosis and therapeutic resistance (X. Li et al., 2013; Wong et al., 2023). In addition, the SOX family is involved in the formation of the tumor immune microenvironment (TIME), regulating the differentiation, activation, and release of chemokines of immune cells, which affects the immune escape and immunotherapy efficacy of tumors (Kuwahara et al., 2012; Yang et al., 2016). Studies have also found that SOX family members can be regulated by epigenetic modifications and non-coding RNAs, affecting the progression of tumors (X. Chen et al., 2020; J.-Y. Li et al., 2012). Therefore, SOX family transcription factors are potential targets for cancer treatment, and therapeutic strategies targeting them are being actively explored, including the development of drugs that directly target SOX proteins and SOX-based immunotherapies (Liu et al., 2023; Ruzinova et al., 2023).

The SOX gene family plays a significant role in OSCC. A study demonstrated that high levels of SOX2 may indicate local spreading in patients with OSCC, while silencing the SOX2 gene can enhance the sensitivity of OSCC cells to cisplatin and inhibit their migration ability and cancer stem cell characteristics (Sacco et al., 2023).

Sox2, as an oncogene, is associated with maintaining the undifferentiated state of tumor stem cells (Luiz et al., 2018). The role of Sox4 in OSCC is controversial, but some studies have indicated that it may promote tumor development (Liu et al., 2016; Rosa et al., 2015, 2018). The transcription level of Sox7 in OSCC tissue is significantly lower than that in normal tissue, and the low level of Sox7 is significantly correlated with low tumor differentiation, advanced staging, and positive lymph node metastasis (D. Chen et al., 2018).The high expression of Sox8 isival rate (S.-L. Xie et al., 2018). SOX9 gene is highly expressed in oral cancer and might be potential therapeutic targets for oral cancer, and the poor overall survival of patients with the high expression of SOX9 (T. Li et al., 2023). A study indicated that the DNA hypomethylation-associated upregulation of Sox11 could promote oncogenic transformation via the PI3K/AKT pathway in OLP-associated OSCC (Liu et al., 2024). Therefore, Sox11 might be a reliable biomarker for predicting the progression of precancerous oral tissues (Liu et al., 2024). These findings not only reveal the complex mechanisms of Sox genes in OSCC but also provide new targets and biomarkers for future diagnosis and treatment.

3.2 HIF-1α

Hypoxia-inducible factor-1 (HIF-1) is a crucial transcription factor in the cellular response to hypoxia, composed of a heterodimer of β subunits and α subunits (Schofield & Ratcliffe, 2005). HIF-1α, as one of the most important transcriptional molecules of the α subunits, participates in the occurrence and progression of tumors through genetic diversity as well as environmental mechanisms and hypoxic stimulation, making the upregulation of HIF-1α particularly noteworthy compared to other subtypes (H.-S. Li et al., 2019). The formation of a hypoxic microenvironment can upregulate the expression of hypoxia-inducible factor 1 in tumor cells. As a transcription factor, HIF-1 can bind to the hypoxia response elements in the promoter region of target genes, thereby upregulating the expression of these genes. This leads to the inhibition of tumor cell apoptosis, promotion of tumor cell proliferation, and enhancement of tumor cell migration and invasion (Ebright et al., 2020; Gao et al., 2023; Hong et al., 2019; Shi et al., 2021; Zhong et al., 2022). In tongue cancer, the expression of HIF-1α has been identified as a standalone prognostic indicator (Kang et al., 2013). Christian Wilhelm and colleagues confirmed that the transcription factor HIF-1α is a relevant hypoxia-dependent oncogenic regulator in HNSCC (Wilhelm et al., 2021).

Ambika Murugesan et al. found that the expression of both HIF and Nestin has significant implications around metastatic OSCC (Murugesan et al., 2024). Sumera Sumera et al. conducted research indicating that increased expression of HIF-1α is a tumor-specific finding, with minimal or no expression in normal oral tissues. Assessing the overexpression of HIF-1α in OSCCs can enhance diagnostic accuracy (Sumera et al., 2023).

3.3 E-cadherin

The epithelial-to-mesenchymal transition (EMT) theory provides a good explanation for the occurrence, development, invasion, and metastasis of tumors, and thus has attracted increasing attention. EMT refers to a process in which epithelial cells undergo a morphological transformation towards a mesenchymal cell phenotype while acquiring migratory capabilities (Acloque et al., 2009) . Studies have shown that tumors with strong metastatic potential, such as OSCC, exhibit EMT phenomena, and the occurrence of EMT may contribute to the progression of OSCC and is closely related to its prognosis (Chaw et al., 2012; Elhosary et al., 2024; Sakamoto et al., 2012). By monitoring the occurrence of EMT, it may be possible to detect early OSCC, thereby improving patients' survival rates. E-cadherin is an important marker in the EMT process, a calcium-dependent transmembrane protein that links extracellular immunoglobulin domains and is involved in cell-to-cell adhesion. It plays a crucial role in maintaining cell polarity and integrity. Diniz-Freitas M et al. discovered that the invasive behavior of tumor cells can be significantly inhibited by transfecting E-cadherin protein, and they consider the reduction of E-cadherin expression to be a sign of malignancy (Diniz-Freitas et al., 2006). Ilena S Yim et al. also confirmed that molecular markers of EMT, including TWIST, vimentin, and N-cadherin, can serve as prognostic markers for oral cancer(Yim & Laronde, 2024). Subsequent extensive research data has also shown that the expression of E-cadherin is reduced in squamous cell carcinoma (SCC) or at the invasive front of SCC (Afrem et al., 2014; Costa et al., 2015; da Cunha et al., 2016; Diniz-Freitas et al., 2006).

3.4 CCND1 and other proteins

Cyclin D1 (CCND1) plays a vital role in promoting cell proliferation, and its mutations or deficiencies can lead to cell-cycle arrest and apoptosis (G. Chen et al., 2019; Sun et al., 2019; Xu et al., 2020). Notably, CCND1 acts as an oncogene that facilitates the progression of various cancers, including colorectal cancer (Albasri et al., 2019), breast cancer (Choi et al., 2019) and OSCC (Kujan et al., 2019; Ramos-García et al., 2019). Interestingly, studies have shown that silencing CCND1 is an effective approach to inhibit the progression of OSCC. Researchers have constructed a risk model associated with HNSCC (Ding et al., 2023), which includes 9 gene sets: CXCL13, MORF4L2, CTSL1, TMEM173, TBC1D2, WIPF1, C5orf15, LIPA, and ISG20. The results indicate that high expression of ISG20 and CTSL1 is positively correlated with poor prognosis in cancer patients, and ISG20 can promote angiogenesis, tumor cell proliferation, and metastasis. In addition, high expression of CXCL13 in tumors is associated with the prognosis of various cancers, including oral squamous cell carcinoma and breast cancer. TMEM173 is related to the clinical condition and immune response of HNSCC patients and can serve as a biological marker to improve patient prognosis. In HNSCC, 30% of the activated signaling pathways is the PI3K pathway, and genes encoding tyrosine kinase receptors involved in tumorigenesis (such as IGF1R, DDR2, EGFR, EPHB2, FGFR1, FGFR2, FGFR3, ERBB2, or MET) are also activated to

varying degrees (Saada-Bouzid et al., 2019).

3.5 Long non-coding RNAs biomarkers for TSCC

Long non-coding RNA (LncRNA) plays a regulatory role in protein expression on multiple levels (epigenetic regulation, transcriptional regulation, and post-transcriptional regulation), thereby influencing the occurrence and development of tumors (Folkins et al., 2009; Kaur et al., 2003; Saidi et al., 2008). Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) is one of the earliest discovered lncRNAs. Initially identified in non-small cell lung cancer through subtractive hybridization, it is approximately 8700 base pairs in length and located on human chromosome 11q13 (P. Ji et al., 2003)。It is overexpressed or mutated in various human malignant tumors such as breast cancer, renal cell carcinoma, non-small cell lung cancer, colon cancer, liver cancer, cervical cancer, and is associated with prognosis. Rania Shalaby et al. found that the long non-coding RNA MALAT1 is underexpressed in meningiomas and correlates with heightened tumor aggressiveness (Elhosary et al., 2024). Jing Ning et al. found that the overexpression of lncRNA MALAT1 enhanced the viability, proliferation, and invasive capabilities of multiple myeloma (MM) cells (Ning et al., 2024). In tissues affected by COPD and lung cancer, the expression of MALAT1 is elevated, and it facilitates tumor invasion and metastasis by modulating alternative splicing and gene expression patterns that are linked to the advancement of metastasis (Sweef et al., 2024). MALAT1 enhanced the proliferation, migration, and invasion of NSCLC cells and hindered apoptosis by modulating the expression of MDM4 through the action of miR-185-5p (D. Wang et al., 2020). Xuan Zhou et al. analyzed 96 OSCC specimens and found that the expression of MALAT1 in OSCC tissues was significantly higher than in normal oral tissues. Moreover, high expression of MALAT1 was closely associated with poor patient prognosis (Zhou et al., 2015).Salivary lncRNA MALAT1 serves as a miRNA-124 sponge and may represent a promising saliva-based biomarker for the detection of OSCC (Shalaby et al., 2024).

4. Conclusion

Genetic and protein biomarkers such as TP53, NOTCH1, P16INK4a, members of the SOX family, HIF-1α, E-cadherin, and CCND1 play a crucial role in the occurrence, progression, and prognostic assessment of OSCC. In addition, long non-coding RNAs (LncRNAs), particularly MALAT1, also have a significant impact on the regulation of OSCC and could potentially act as indicators for diagnosis and assessment of disease progression. These biomarkers not only help us to gain a deeper understanding of the tumor biology characteristics of OSCC but also provide new perspectives for early diagnosis, prognostic assessment, and personalized treatment. Further research is needed to explore the clinical applications of these biomarkers in order to improve the treatment outcomes and quality of life for patients with OSCC.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The English language of the article was improved with ChatGPT. Upon generating draft language, the author reviewed, edited and revised the language to their own liking and takes ultimate responsibility for the content of this publication.

AVAILABILITY OF DATA AND MATERIALS

The datasets supporting the conclusions of this article are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Research Management Centre, MAHSA University (RMC/DECEMBER/2024/EC05) and the Medical Ethics Committee of Youjiang Medical University for Nationalities (approval number: 2024091101).

HUMAN AND ANIMAL RIGHTS

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CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare that none of them has any conflict of interest.

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[1] Abby, E., Dentro, S. C., Hall, M. W. J., Fowler, J. C., Ong, S. H., Sood, R., Herms, A., Piedrafita, G., Abnizova, I., Siebel, C. W., Gerstung, M., Hall, B. A., & Jones, P. H. (2023). Notch1 mutations drive clonal expansion in normal esophageal epithelium but impair tumor growth. Nature Genetics, 55(2), 232–245. https://doi.org/10.1038/s41588-022-01280-z

[2] Acloque, H., Adams, M. S., Fishwick, K., Bronner-Fraser, M., & Nieto, M. A. (2009). Epithelial-mesenchymal transitions: The importance of changing cell state in development and disease. The Journal of Clinical Investigation, 119(6), 1438–1449. https://doi.org/10.1172/JCI38019

[3] Afrem, M. C., Mărgăritescu, C., Crăiţoiu, M. M., Ciucă, M., Şarlă, C. G., & Cotoi, O. S. (2014). The immunohistochemical investigations of cadherin "switch" during epithelial-mesenchymal transition of tongue squamous cell carcinoma. Romanian Journal of Morphology and Embryology = Revue Roumaine De Morphologie Et Embryologie, 55(3 Suppl), 1049–1056.

[4] Agrawal, N., Frederick, M. J., Pickering, C. R., Bettegowda, C., Chang, K., Li, R. J., Fakhry, C., Xie, T.-X., Zhang, J., Wang, J., Zhang, N., El-Naggar, A. K., Jasser, S. A., Weinstein, J. N., Treviño, L., Drummond, J. A., Muzny, D. M., Wu, Y., Wood, L. D., … Myers, J. N. (2011). Exome Sequencing of Head and Neck Squamous Cell Carcinoma Reveals Inactivating Mutations in NOTCH1. Science, 333(6046), 1154–1157. https://doi.org/10.1126/science.1206923

[5] Albasri, A. M., Elkablawy, M. A., Ansari, I. A., & Alhujaily, A. S. (2019). Prognostic Significance of Cyclin D1 Over-expression in Colorectal Cancer: An Experience from Madinah, Saudi Arabia. Asian Pacific Journal of Cancer Prevention: APJCP, 20(8), 2471–2476. https://doi.org/10.31557/APJCP.2019.20.8.2471

[6] Artavanis-Tsakonas, S. (1988). The molecular biology of the Notch locus and the fine tuning of differentiation in Drosophila. Trends in Genetics, 4(4), 95–100. https://doi.org/10.1016/0168-9525(88)90096-0

[7] Bakker, E., Starokozhko, V., Kraaijvanger, J. W. M., Heerspink, H. J. L., & Mol, P. G. M. (2023). Precision medicine in regulatory decision making: Biomarkers used for patient selection in European Public Assessment Reports from 2018 to 2020. Clinical and Translational Science, 16(11), 2394–2412. https://doi.org/10.1111/cts.13641

[8] Berglund, A., Muenyi, C., Siegel, E. M., Ajidahun, A., Eschrich, S. A., Wong, D., Hendrick, L. E., Putney, R. M., Kim, S., Hayes, D. N., & Shibata, D. (2022). Characterization of Epigenomic Alterations in HPV16+ Head and Neck Squamous Cell Carcinomas. Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 31(4), 858–869. https://doi.org/10.1158/1055-9965.EPI-21-0922

[9] Betz, S. J. (2019). HPV-Related Papillary Lesions of the Oral Mucosa: A Review. Head and Neck Pathology, 13(1), 80–90. https://doi.org/10.1007/s12105-019-01003-7

[10] Brooks, Y. S., Ostano, P., Jo, S.-H., Dai, J., Getsios, S., Dziunycz, P., Hofbauer, G. F. L., Cerveny, K., Chiorino, G., Lefort, K., & Dotto, G. P. (2014). Multifactorial ERβ and NOTCH1 control of squamous differentiation and cancer. The Journal of Clinical Investigation, 124(5), 2260–2276. https://doi.org/10.1172/JCI72718

[11] Chaw, S. Y., Abdul Majeed, A., Dalley, A. J., Chan, A., Stein, S., & Farah, C. S. (2012). Epithelial to mesenchymal transition (EMT) biomarkers—E-cadherin, beta-catenin, APC and Vimentin—In oral squamous cell carcinogenesis and transformation. Oral Oncology, 48(10), 997–1006. https://doi.org/10.1016/j.oraloncology.2012.05.011

[12] Chen, D., Li, J., Li, S., Han, P., Li, N., Wang, Y., & Du, S. (2018). miR-184 promotes cell proliferation in tongue squamous cell carcinoma by targeting SOX7. Oncology Letters. https://doi.org/10.3892/ol.2018.8906

[13] Chen, G., Ding, X.-F., Bouamar, H., Pressley, K., & Sun, L.-Z. (2019). Everolimus induces G1 cell cycle arrest through autophagy-mediated protein degradation of cyclin D1 in breast cancer cells. American Journal of Physiology. Cell Physiology, 317(2), C244–C252. https://doi.org/10.1152/ajpcell.00390.2018

[14] Chen, X., Xu, M., Xu, X., Zeng, K., Liu, X., Pan, B., Li, C., Sun, L., Qin, J., Xu, T., He, B., Pan, Y., Sun, H., & Wang, S. (2020). METTL14-mediated N6-methyladenosine modification of SOX4 mRNA inhibits tumor metastasis in colorectal cancer. Molecular Cancer, 19(1), 106. https://doi.org/10.1186/s12943-020-01220-7

[15] Choi, C., Park, S., Cho, W. K., & Choi, D. H. (2019). Cyclin D1 is Associated with Radiosensitivity of Triple-Negative Breast Cancer Cells to Proton Beam Irradiation. International Journal of Molecular Sciences, 20(19), 4943. https://doi.org/10.3390/ijms20194943

[16] Costa, L. C. M. C., Leite, C. F., Cardoso, S. V., Loyola, A. M., Faria, P. R. de, Souza, P. E. A., & Horta, M. C. R. (2015). Expression of epithelial-mesenchymal transition markers at the invasive front of oral squamous cell carcinoma. Journal of Applied Oral Science: Revista FOB, 23(2), 169–178. https://doi.org/10.1590/1678-775720140187

[17] da Cunha, I. W., Souza, M. J. L., da Costa, W. H., Amâncio, A. M., Fonseca, F. P., Zequi, S. de C., Lopes, A., Guimarães, G. C., & Soares, F. (2016). Epithelial-mesenchymal transition (EMT) phenotype at invasion front of squamous cell carcinoma of the penis influences oncological outcomes. Urologic Oncology, 34(10), 433.e19-26. https://doi.org/10.1016/j.urolonc.2016.05.015

[18] Da Silva, A. M., Falcão, M. M. L., Freitas, V. S., & Vieira, A. R. (2024). Genetic and environmental contributions for the relationship between tooth loss and oral potentially malignant disorders and oral squamous cell carcinoma. Head & Neck, 46(6), 1417–1427. https://doi.org/10.1002/hed.27648

[19] Ding, Y., Chu, L., Cao, Q., Lei, H., Li, X., & Zhuang, Q. (2023). A meta-validated immune infiltration-related gene model predicts prognosis and immunotherapy sensitivity in HNSCC. BMC Cancer, 23(1), 45. https://doi.org/10.1186/s12885-023-10532-y

[20] Diniz-Freitas, M., García-Caballero, T., Antúnez-López, J., Gándara-Rey, J. M., & García-García, A. (2006). Reduced E-cadherin expression is an indicator of unfavourable prognosis in oral squamous cell carcinoma. Oral Oncology, 42(2), 190–200. https://doi.org/10.1016/j.oraloncology.2005.07.010

[21] Ebright, R. Y., Zachariah, M. A., Micalizzi, D. S., Wittner, B. S., Niederhoffer, K. L., Nieman, L. T., Chirn, B., Wiley, D. F., Wesley, B., Shaw, B., Nieblas-Bedolla, E., Atlas, L., Szabolcs, A., Iafrate, A. J., Toner, M., Ting, D. T., Brastianos, P. K., Haber, D. A., & Maheswaran, S. (2020). HIF1A signaling selectively supports proliferation of breast cancer in the brain. Nature Communications, 11(1), 6311. https://doi.org/10.1038/s41467-020-20144-w

[22] Elhosary, E., Shibel, P. E. E., Eltoukhy, M., Talaat, R., Kamel, M., & Soliman, N. A. (2024). Downregulation of lncRNA-MALAT1, Altered Immunohistochemical Expression of Cyclin D1 Protein and E-Cadherin Protein in Correlation to Meningioma Grades. Asian Pacific Journal of Cancer Prevention: APJCP, 25(11), 4097–4107. https://doi.org/10.31557/APJCP.2024.25.11.4097

[23] Ellisen, L. W., Bird, J., West, D. C., Soreng, A. L., Reynolds, T. C., Smith, S. D., & Sklar, J. (1991). TAN-1, the human homolog of the Drosophila Notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. Cell, 66(4), 649–661. https://doi.org/10.1016/0092-8674(91)90111-B

[24] Folkins, C., Shaked, Y., Man, S., Tang, T., Lee, C. R., Zhu, Z., Hoffman, R. M., & Kerbel, R. S. (2009). Glioma tumor stem-like cells promote tumor angiogenesis and vasculogenesis via vascular endothelial

growth factor and stromal-derived factor 1. Cancer Research, 69(18), 7243–7251. https://doi.org/10.1158/0008-5472.CAN-09-0167

[25] Gao, S., Zhang, W., Ma, J., & Ni, X. (2023). PHF6 recruits BPTF to promote HIF-dependent pathway and progression in YAP-high breast cancer. Journal of Translational Medicine, 21, 220. https://doi.org/10.1186/s12967-023-04031-8

[26] Grilli, G., Hermida-Prado, F., Álvarez-Fernández, M., Allonca, E., Álvarez-González, M., Astudillo, A., Moreno-Bueno, G., Cano, A., García-Pedrero, J. M., & Rodrigo, J. P. (2020). Impact of notch signaling on the prognosis of patients with head and neck squamous cell carcinoma. Oral Oncology, 110, 105003. https://doi.org/10.1016/j.oraloncology.2020.105003

[27] Hakeem, A., Fitzpatrick, S. G., Gonsalves, C. A., Isom, J., Islam, M. N., Bhattacharyya, I., Cohen, D. M., & Drew, P. A. (2020). p16INK4a as a proliferation marker unrelated to HPV expression in odontogenic cysts and tumors. Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 49(1), 72–81. https://doi.org/10.1111/jop.12972

[28] Hakeem, A., Fitzpatrick, S. G., Gonsalves, C. A., Isom, J., Islam, M. N., Bhattacharyya, I., Cohen, D. M., & Drew, P. A. (2020). p16INK4a as a proliferation marker unrelated to HPV expression in odontogenic cysts and tumors. Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 49(1), 72–81. https://doi.org/10.1111/jop.12972

[29] Inamura, N., Kimura, T., Wang, L., Yanagi, H., Tsuda, M., Tanino, M., Nishihara, H., Fukuda, S., & Tanaka, S. (2017). Notch1 regulates invasion and metastasis of head and neck squamous cell carcinoma by inducing EMT through c-Myc. Auris Nasus Larynx, 44(4), 447–457. https://doi.org/10.1016/j.anl.2016.08.003

[30] Jafari, N., Abediankenari, S., Hosseini-Khah, Z., Valizadeh, S. M., Torabizadeh, Z., Zaboli, E., Ghasemi, M., Fakheri, H., Hosseini, V., Shekarriz, R., Rafiei, A., Asgarian-Omran, H., & Abedian, F. (2020). Expression patterns of seven key genes, including β-catenin, Notch1, GATA6, CDX2, miR-34a, miR-181a and miR-93 in gastric cancer. Scientific Reports, 10(1), 12342. https://doi.org/10.1038/s41598-020-69308-0

[31] Ji, J. H., Bae, S. J., Kim, K., Chu, C., Lee, K.-A., Kim, Y., Kim, J. H., Jeong, J., & Ahn, S. G. (2022). Association between TP53 mutation and high 21-gene recurrence score in estrogen receptor-positive/HER2-negative breast cancer. NPJ Breast Cancer, 8, 19. https://doi.org/10.1038/s41523-022-00384-3

[32] Ji, P., Diederichs, S., Wang, W., Böing, S., Metzger, R., Schneider, P. M., Tidow, N., Brandt, B., Buerger, H., Bulk, E., Thomas, M., Berdel, W. E., Serve, H., & Müller-Tidow, C. (2003). MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene, 22(39), 8031–8041. https://doi.org/10.1038/sj.onc.1206928

[33] Jiao, J., Qin, Z., Li, S., Liu, H., & Lu, Z. (2009). Potential role of Notch1 signaling pathway in laryngeal squamous cell carcinoma cell line Hep-2 involving proliferation inhibition, cell cycle arrest, cell apoptosis, and cell migration. Oncology Reports, 22(4), 815–823. https://doi.org/10.3892/or_00000504

[34] Jiao, X., Wood, L. D., Lindman, M., Jones, S., Buckhaults, P., Polyak, K., Sukumar, S., Carter, H., Kim, D., Karchin, R., & Sjöblom, T. (2012). Somatic mutations in the notch, NF-KB, PIK3CA, and hedgehog pathways in human breast cancers. Genes, Chromosomes and Cancer, 51(5), 480–489. https://doi.org/10.1002/gcc.21935

[35] Kaka, A. S., Nowacki, N. B., Kumar, B., Zhao, S., Old, M. O., Agrawal, A., Ozer, E., Carrau, R. L., Schuller, D. E., Kumar, P., & Teknos, T. N. (2017). Notch1 Overexpression Correlates to Improved Survival in Cancer of the Oropharynx. Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck

Surgery, 156(4), 652–659. https://doi.org/10.1177/0194599816688178

[36] Kang, F.-W., Gao, Y., Que, L., Sun, J., & Wang, Z.-L. (2013). Hypoxia-inducible factor-1α overexpression indicates poor clinical outcomes in tongue squamous cell carcinoma. Experimental and Therapeutic Medicine, 5(1), 112–118. https://doi.org/10.3892/etm.2012.779

[37] Kaur, B., Brat, D. J., Calkins, C. C., & Van Meir, E. G. (2003). Brain angiogenesis inhibitor 1 is differentially expressed in normal brain and glioblastoma independently of p53 expression. The American Journal of Pathology, 162(1), 19–27. https://doi.org/10.1016/S0002-9440(10)63794-7

[38] Kravets, O., Burtyn, O., Borikun, T., & Rossylna, O. (2023). THE STUDY OF PROGNOSTIC VALUE OF microRNAs (miR-10b AND -155) AND CDKN2A/P16INK4A IN ORAL SQUAMOUS CELL CARCINOMA. Experimental Oncology, 45(2), 187–194. https://doi.org/10.15407/exp-oncology.2023.02.187

[39] Kujan, O., Huang, G., Ravindran, A., Vijayan, M., & Farah, C. S. (2019). CDK4, CDK6, cyclin D1 and Notch1 immunocytochemical expression of oral brush liquid-based cytology for the diagnosis of oral leukoplakia and oral cancer. Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 48(7), 566–573. https://doi.org/10.1111/jop.12902

[40] Kuwahara, M., Yamashita, M., Shinoda, K., Tofukuji, S., Onodera, A., Shinnakasu, R., Motohashi, S., Hosokawa, H., Tumes, D., Iwamura, C., Lefebvre, V., & Nakayama, T. (2012). The transcription factor Sox4 is a downstream target of signaling by the cytokine TGF-β and suppresses T(H)2 differentiation. Nature Immunology, 13(8), 778–786. https://doi.org/10.1038/ni.2362

[41] Lee, S. H., Do, S. I., Lee, H. J., Kang, H. J., Koo, B. S., & Lim, Y. C. (2016). Notch1 signaling contributes to stemness in head and neck squamous cell carcinoma. Laboratory Investigation; a Journal of Technical Methods and Pathology, 96(5), 508–516. https://doi.org/10.1038/labinvest.2015.163

[42] Leong, K. G., & Karsan, A. (2006). Recent insights into the role of Notch signaling in tumorigenesis. Blood, 107(6), 2223–2233. https://doi.org/10.1182/blood-2005-08-3329

[43] Li, H.-S., Zhou, Y.-N., Li, L., Li, S.-F., Long, D., Chen, X.-L., Zhang, J.-B., Feng, L., & Li, Y.-P. (2019). HIF-1α protects against oxidative stress by directly targeting mitochondria. Redox Biology, 25, 101109. https://doi.org/10.1016/j.redox.2019.101109

[44] Li, J.-Y., Han, C., Zheng, L.-L., & Guo, M.-Z. (2012). Epigenetic regulation of Wnt signaling pathway gene SRY-related HMG-box 17 in papillary thyroid carcinoma. Chinese Medical Journal, 125(19), 3526–3531.

[45] Li, T., Cheng, D., Guo, J., Chen, H., Zhang, S., & Bao, Y. (2023). SOX9 and IL1A as the Potential Gene Biomarkers of the Oral Cancer. Combinatorial Chemistry & High Throughput Screening, 26(8), 1461–1479. https://doi.org/10.2174/1386207325666220628091041

[46] Li, X., Xu, Y., Chen, Y., Chen, S., Jia, X., Sun, T., Liu, Y., Li, X., Xiang, R., & Li, N. (2013). SOX2 promotes tumor metastasis by stimulating epithelial-to-mesenchymal transition via regulation of WNT/β-catenin signal network. Cancer Letters, 336(2), 379–389. https://doi.org/10.1016/j.canlet.2013.03.027

[47] Liu, Y., Cao, P., Xiao, L., Tang, N., Fei, W., & Li, X. (2024). Hypomethylation-associated Sox11 upregulation promotes oncogenesis via the PI3K/AKT pathway in OLP-associated OSCC. Journal of Cellular and Molecular Medicine, 28(14), e18556. https://doi.org/10.1111/jcmm.18556

[48] Liu, Y., Cui, L., Huang, J., Ji, E. H., Chen, W., Messadi, D., & Hu, S. (2016). SOX4 Promotes Progression in OLP-Associated Squamous Cell Carcinoma. Journal of Cancer, 7(11), 1534–1540. https://doi.org/10.7150/jca.15689

[49] Liu, Y., Keib, A., Neuber, B., Wang, L.,

Riemer, A. B., Bonsack, M., Hückelhoven-Krauss, A., Schmitt, A., Müller-Tidow, C., & Schmitt, M. (2023). Definition and Characterization of SOX11-Derived T Cell Epitopes towards Immunotherapy of Glioma. International Journal of Molecular Sciences, 24(3), 1943. https://doi.org/10.3390/ijms24031943

[50] Luiz, S. T., Modolo, F., Mozzer, I., Dos Santos, E. C., Nagashima, S., Camargo Martins, A. P., de Azevedo, M. L. V., Azevedo Alanis, L. R., Hardy, A. M. T. G., de Moraes, R. S., Aguiar, M. C. F., Ignácio, S. A., Jham, B. C., Noronha, L., & Johann, A. C. B. R. (2018). Immunoexpression of SOX-2 in oral leukoplakia. Oral Diseases, 24(8), 1449–1457. https://doi.org/10.1111/odi.12922

[51] Ma, P., Sf, G., F, G., Mj, D., Pyf, Z., H, M., Jw, B., Ac, N., & Js, M. (2020). Survival-Associated Metabolic Genes in Human Papillomavirus-Positive Head and Neck Cancers. Cancers, 12(1). https://doi.org/10.3390/cancers12010253

[52] Mao, L., Zhao, Z.-L., Yu, G.-T., Wu, L., Deng, W.-W., Li, Y.-C., Liu, J.-F., Bu, L.-L., Liu, B., Kulkarni, A. B., Zhang, W.-F., Zhang, L., & Sun, Z.-J. (2018). γ-Secretase inhibitor reduces immunosuppressive cells and enhances tumour immunity in head and neck squamous cell carcinoma. International Journal of Cancer, 142(5), 999–1009. https://doi.org/10.1002/ijc.31115

[53] Morand, G. B., Diaconescu, A., Ibrahim, I., Lamarche, G., Ruas, J. S., Dalfen, J., Hier, M. P., Alaoui-Jamali, M. A., Maschietto, M., & da Silva, S. D. (2022). Molecular prognostic indicators in HPV-positive oropharyngeal cancer: An updated review. Clinical & Experimental Metastasis, 39(3), 407–416. https://doi.org/10.1007/s10585-022-10148-9

[54] Morita, S., Nakamaru, Y., Homma, A., Yasukawa, S., Hatakeyama, H., Sakashita, T., Kano, S., Fukuda, A., & Fukuda, S. (2017). Expression of p53, p16, cyclin D1, epidermal growth factor receptor and Notch1 in patients with temporal bone squamous cell carcinoma. International Journal of Clinical Oncology, 22(1), 181–189. https://doi.org/10.1007/s10147-016-1026-5

[55] Murugesan, A., Bharath, C., Balakrishnan, S., Kandasamy, S., Priyadharshini, I., & Ravi, S. (2024). Expression of HIF-1α and Nestin in oral squamous cell carcinoma and its association with vasculogenic mimicry. Journal of Cancer Research and Therapeutics, 20(1), 176–180. https://doi.org/10.4103/jcrt.jcrt_1834_22

[56] Ning, J., Yang, R., Wang, H., Ma, H., & Cui, L. (2024). LncRNA MALAT1 silencing represses CXCL12-induced proliferation, invasion, and homing behavior in multiple myeloma by inhibiting CXCR4. Hematology (Amsterdam, Netherlands), 29(1), 2422154. https://doi.org/10.1080/16078454.2024.2422154

[57] Nyman, P. E., Buehler, D., & Lambert, P. F. (2018). Loss of Function of Canonical Notch Signaling Drives Head and Neck Carcinogenesis. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 24(24), 6308–6318. https://doi.org/10.1158/1078-0432.CCR-17-3535

[58] Pang, Y., Sun, Y., Wu, Y., Li, J., Qin, P., Guo, S., Zhou, W., Chen, J., & Wang, J. (2024). Targeting the ZMIZ1-Notch1 signaling axis for the treatment of tongue squamous cell carcinoma. Scientific Reports, 14, 13577. https://doi.org/10.1038/s41598-024-59882-y

[59] Pickering, C. R., Zhang, J., Yoo, S. Y., Bengtsson, L., Moorthy, S., Neskey, D. M., Zhao, M., Ortega Alves, M. V., Chang, K., Drummond, J., Cortez, E., Xie, T.-X., Zhang, D., Chung, W., Issa, J.-P. J., Zweidler-McKay, P. A., Wu, X., El-Naggar, A. K., Weinstein, J. N., … Frederick, M. J. (2013). Integrative genomic characterization of oral squamous cell carcinoma identifies frequent somatic drivers. Cancer Discovery, 3(7), 770–781. https://doi.org/10.1158/2159-8290.CD-12-0537

[60] Puente, X. S., Pinyol, M., Quesada, V., Conde, L., Ordóñez, G. R., Villamor, N., Escaramis, G., Jares, P., Beà, S., González-Díaz, M., Bassaganyas, L., Baumann, T., Juan, M., López-Guerra, M., Colomer, D., Tubío, J. M. C., López, C., Navarro, A., Tornador, C., … Campo, E. (2011). Whole-genome sequencing identifies recurrent

mutations in chronic lymphocytic leukaemia. Nature, 475(7354), 101–105. https://doi.org/10.1038/nature10113

[61] Ramos-García, P., González-Moles, M. Á., González-Ruiz, L., Ayén, Á., Ruiz-Ávila, I., Bravo, M., & Gil-Montoya, J. A. (2019). Clinicopathological significance of tumor cyclin D1 expression in oral cancer. Archives of Oral Biology, 99, 177–182. https://doi.org/10.1016/j.archoralbio.2019.01.018

[62] Romanovsky, E., Kluck, K., Ourailidis, I., Menzel, M., Beck, S., Ball, M., Kazdal, D., Christopoulos, P., Schirmacher, P., Stiewe, T., Stenzinger, A., & Budczies, J. (2023). Homogenous TP53mut-associated tumor biology across mutation and cancer types revealed by transcriptome analysis. Cell Death Discovery, 9(1), 126. https://doi.org/10.1038/s41420-023-01413-1

[63] Rosa, E. A., Hurtado-Puerto, A. M., Falcão, D. P., Brietzke, A. P., De Almeida Prado Franceschi, L. E., Cavalcanti Neto, F. F., Tiziane, V., Carneiro, F. P., Kogawa, E. M., Moreno, H., & Amorim, R. F. B. (2018). Oral lichen planus and malignant transformation: The role of p16, Ki-67, Bub-3 and SOX4 in assessing precancerous potential. Experimental and Therapeutic Medicine, 15(5), 4157–4166. https://doi.org/10.3892/etm.2018.5971

[64] Rosa, E. A., Lia, E. N., Macedo, S. B., & Amorim, R. F. B. de. (2015). In situ carcinoma developed over oral lichen planus: A case report with analysis of BUB3, p16, p53, Ki67 and SOX4 expression. Journal of Applied Oral Science: Revista FOB, 23(4), 442–447. https://doi.org/10.1590/1678-775720150058

[65] Ruzinova, M. B., Ma, C., Brunt, E. M., Goss, C. W., Vachharajani, N., Chapman, W. C., & Liu, T.-C. (2023). SOX9 Expression Is Superior to Other Stem Cell Markers K19 and EpCAM in Predicting Prognosis in Hepatocellular Carcinoma. The American Journal of Surgical Pathology, 47(1), 1–11. https://doi.org/10.1097/PAS.0000000000001990

[66] Saada-Bouzid, E., Peyrade, F., & Guigay, J. (2019). Molecular genetics of head and neck squamous cell carcinoma. Current Opinion in Oncology, 31(3), 131–137. https://doi.org/10.1097/CCO.0000000000000536

[67] Sacco, A., Battaglia, A. M., Santamaria, G., Buffone, C., Barone, S., Procopio, A., Lavecchia, A. M., Aversa, I., Giorgio, E., Petriaggi, L., Cristofaro, M. G., Biamonte, F., & Giudice, A. (2023). SOX2 promotes a cancer stem cell-like phenotype and local spreading in oral squamous cell carcinoma. PLOS ONE, 18(12), e0293475. https://doi.org/10.1371/journal.pone.0293475

[68] Saidi, A., Javerzat, S., Bellahcène, A., De Vos, J., Bello, L., Castronovo, V., Deprez, M., Loiseau, H., Bikfalvi, A., & Hagedorn, M. (2008). Experimental anti-angiogenesis causes upregulation of genes associated with poor survival in glioblastoma. International Journal of Cancer, 122(10), 2187–2198. https://doi.org/10.1002/ijc.23313

[69] Saidi, A., Javerzat, S., Bellahcène, A., De Vos, J., Bello, L., Castronovo, V., Deprez, M., Loiseau, H., Bikfalvi, A., & Hagedorn, M. (2008). Experimental anti-angiogenesis causes upregulation of genes associated with poor survival in glioblastoma. International Journal of Cancer, 122(10), 2187–2198. https://doi.org/10.1002/ijc.23313

[70] Schmidl, B., Siegl, M., Boxberg, M., Stögbauer, F., Jira, D., Winter, C., Stark, L., Pickhard, A., Wollenberg, B., & Wirth, M. (2022). NOTCH1 Intracellular Domain and the Tumor Microenvironment as Prognostic Markers in HNSCC. Cancers, 14(4), 1080. https://doi.org/10.3390/cancers14041080

[71] Schofield, C. J., & Ratcliffe, P. J. (2005). Signalling hypoxia by HIF hydroxylases. Biochemical and Biophysical Research Communications, 338(1), 617–626. https://doi.org/10.1016/j.bbrc.2005.08.111

[72] Shalaby, R., Ibrahim, S., Kotb, A. A. W., Baz, S., Hafed, L., Shaker, O., & Afifi, S. (2024). MALAT1 as a potential salivary biomarker in oral squamous cell carcinoma through targeting miRNA-124. Oral Diseases, 30(4), 2075–2083. https://doi.org/10.1111/odi.14730

[73] Shi, R., Liao, C., & Zhang, Q. (2021). Hypoxia-Driven Effects in Cancer: Characterization, Mechanisms, and Therapeutic Implications. Cells, 10(3), 678. https://doi.org/10.3390/cells10030678

[74] Stransky, N., Egloff, A. M., Tward, A. D., Kostic, A. D., Cibulskis, K., Sivachenko, A., Kryukov, G. V., Lawrence, M. S., Sougnez, C., McKenna, A., Shefler, E., Ramos, A. H., Stojanov, P., Carter, S. L., Voet, D., Cortés, M. L., Auclair, D., Berger, M. F., Saksena, G., … Grandis, J. R. (2011). The Mutational Landscape of Head and Neck Squamous Cell Carcinoma. Science, 333(6046), 1157–1160. https://doi.org/10.1126/science.1208130

[75] Sumera, S., Ali, A., Yousafzai, Y. M., Durrani, Z., Alorini, M., Aleem, B., & Zahir, R. (2023). Overexpression of Hypoxia-Inducible Factor-1α and Its Relation with Aggressiveness and Grade of Oral Squamous Cell Carcinoma. Diagnostics (Basel, Switzerland), 13(3), 451. https://doi.org/10.3390/diagnostics13030451

[76] Sun, F., Li, N., Tong, X., Zeng, J., He, S., Gai, T., Bai, Y., Liu, L., Lu, K., Shen, J., Han, M., Lu, C., & Dai, F. (2019). Ara-c induces cell cycle G1/S arrest by inducing upregulation of the INK4 family gene or directly inhibiting the formation of the cell cycle-dependent complex CDK4/cyclin D1. Cell Cycle (Georgetown, Tex.), 18(18), 2293–2306. https://doi.org/10.1080/15384101.2019.1644913

[77] Sweef, O., Mahfouz, R., Taşcıoğlu, T., Albowaidey, A., Abdelmonem, M., Asfar, M., Zaabout, E., Corcino, Y. L., Thomas, V., Choi, E.-S., & Furuta, S. (2024). Decoding LncRNA in COPD: Unveiling Prognostic and Diagnostic Power and Their Driving Role in Lung Cancer Progression. International Journal of Molecular Sciences, 25(16), 9001. https://doi.org/10.3390/ijms25169001

[78] Tang, X., & Chen, Y. (2024). Identification and prognostic analysis of metabolic genes associated with TP53 mutation in multiple myeloma. Hematology (Amsterdam, Netherlands), 29(1), 2377850. https://doi.org/10.1080/16078454.2024.2377850

[79] Tasoulas, J., Farquhar, D. R., Sheth, S., Hackman, T., Yarbrough, W. G., Agala, C. B., Koric, A., Giraldi, L., Fabianova, E., Lissowska, J., Świątkowska, B., Vilensky, M., Wünsch-Filho, V., De Carvalho, M. B., López, R. V. M., Holcátová, I., Serraino, D., Polesel, J., Canova, C., … Amelio, A. L. (2024). Poor oral health influences head and neck cancer patient survival: An International Head and Neck Cancer Epidemiology Consortium pooled analysis. JNCI: Journal of the National Cancer Institute, 116(1), 105–114. https://doi.org/10.1093/jnci/djad156

[80] Thin, K. A., Angsuwatcharakon, P., Edwards, S. W., Mutirangura, A., & Puttipanyalears, C. (2022). Upregulation of p16INK4A in Peripheral White Blood Cells as a Novel Screening Marker for Colorectal Carcinoma. Asian Pacific Journal of Cancer Prevention: APJCP, 23(11), 3753–3761. https://doi.org/10.31557/APJCP.2022.23.11.3753

[81] Tian, J., Liu, X., Liu, X., Jing, P., Sa, N., Wang, H., & Xu, W. (2018). Notch1 serves as a prognostic factor and regulates metastasis via regulating EGFR expression in hypopharyngeal squamous cell carcinoma. OncoTargets and Therapy, 11, 7395–7405. https://doi.org/10.2147/OTT.S175423

[82] Tran, A., Klossner, Q., Crain, T., & Prasad, V. (2020). Shifting, overlapping and expanding use of “precision oncology” terminology: A retrospective literature analysis. BMJ Open, 10(6), e036357. https://doi.org/10.1136/bmjopen-2019-036357

[83] Wang, D., Zhang, S., Zhao, M., & Chen, F. (2020). LncRNA MALAT1 accelerates non-small cell lung cancer progression via regulating miR-185-5p/MDM4 axis. Cancer Medicine, 9(23), 9138–9149. https://doi.org/10.1002/cam4.3570

[84] Wang, N. J., Sanborn, Z., Arnett, K. L., Bayston, L. J., Liao, W., Proby, C. M., Leigh, I. M., Collisson, E. A., Gordon, P. B., Jakkula, L., Pennypacker, S., Zou, Y., Sharma, M., North, J. P., Vemula, S. S., Mauro, T. M., Neuhaus, I. M., Leboit, P. E., Hur, J. S., … Cho, R. J. (2011). Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma.

Proceedings of the National Academy of Sciences of the United States of America, 108(43), 17761–17766. https://doi.org/10.1073/pnas.1114669108

[85] Weaver, A. N., Burch, M. B., Cooper, T. S., Della Manna, D. L., Wei, S., Ojesina, A. I., Rosenthal, E. L., & Yang, E. S. (2016). Notch Signaling Activation Is Associated with Patient Mortality and Increased FGF1-Mediated Invasion in Squamous Cell Carcinoma of the Oral Cavity. Molecular Cancer Research: MCR, 14(9), 883–891. https://doi.org/10.1158/1541-7786.MCR-16-0114

[86] Weng, A. P., Ferrando, A. A., Lee, W., Morris, J. P., Silverman, L. B., Sanchez-Irizarry, C., Blacklow, S. C., Look, A. T., & Aster, J. C. (2004). Activating Mutations of NOTCH1 in Human T Cell Acute Lymphoblastic Leukemia. Science, 306(5694), 269–271. https://doi.org/10.1126/science.1102160

[87] Wilhelm, C., Hackenberg, S., Bregenzer, M., Meyer, T., Gehrke, T., Kleinsasser, N., Hagen, R., & Scherzad, A. (2021). Effect of Hypoxia on Proliferation and the Expression of the Genes HIF-1α and JMJD1A in Head and Neck Squamous Cell Carcinoma Cell Lines. Anticancer Research, 41(1), 113–122. https://doi.org/10.21873/anticanres.14756

[88] Wirth, M., Jira, D., Ott, A., Piontek, G., & Pickhard, A. (2018). High NOTCH1 mRNA Expression Is Associated with Better Survival in HNSCC. International Journal of Molecular Sciences, 19(3), 830. https://doi.org/10.3390/ijms19030830

[89] Wong, T. L. M., Wong, T.-L., Zhou, L., Man, K., Purcell, J., Lee, T. K., Yun, J.-P., & Ma, S. (2023). Protein Tyrosine Kinase 7 (PTK7) Promotes Metastasis in Hepatocellular Carcinoma via SOX9 Regulation and TGF-β Signaling. Cellular and Molecular Gastroenterology and Hepatology, 15(1), 13–37. https://doi.org/10.1016/j.jcmgh.2022.09.015

[90] Wu, M.-H., Lu, R.-Y., Yu, S.-J., Tsai, Y.-Z., Lin, Y.-C., Bai, Z.-Y., Liao, R.-Y., Hsu, Y.-C., Chen, C.-C., & Cai, B.-H. (2022). PTC124 Rescues Nonsense Mutation of Two Tumor Suppressor Genes NOTCH1 and FAT1 to Repress HNSCC Cell Proliferation. Biomedicines, 10(11), 2948. https://doi.org/10.3390/biomedicines10112948

[91] Wu-Chou, Y.-H., Hsieh, C.-H., Liao, C.-T., Lin, Y.-T., Fan, W.-L., & Yang, C.-H. (2021). NOTCH1 mutations as prognostic marker in oral squamous cell carcinoma. Pathology - Research and Practice, 223, 153474. https://doi.org/10.1016/j.prp.2021.153474

[92] Xie, F., Gleue, C. A., Deschaine, M., Dasari, S., Lau, J. S., Sartori-Valinotti, J. C., Meves, A., & Lehman, J. S. (2022). Whole-exome sequencing of transforming oral lichen planus reveals mutations in DNA damage repair and apoptosis pathway genes. Journal of Oral Pathology & Medicine: Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology, 51(4), 395–404. https://doi.org/10.1111/jop.13284

[93] Xie, S.-L., Fan, S., Zhang, S.-Y., Chen, W.-X., Li, Q.-X., Pan, G.-K., Zhang, H.-Q., Wang, W.-W., Weng, B., Zhang, Z., Li, J.-S., & Lin, Z.-Y. (2018). SOX8 regulates cancer stem-like properties and cisplatin-induced EMT in tongue squamous cell carcinoma by acting on the Wnt/β-catenin pathway. International Journal of Cancer, 142(6), 1252–1265. https://doi.org/10.1002/ijc.31134

[94] Xu, S., Zhang, H., Liu, T., Yang, W., Lv, W., He, D., Guo, P., & Li, L. (2020). 6-Gingerol induces cell-cycle G1-phase arrest through AKT-GSK 3β-cyclin D1 pathway in renal-cell carcinoma. Cancer Chemotherapy and Pharmacology, 85(2), 379–390. https://doi.org/10.1007/s00280-019-03999-9

[95] Yang, Y., Andersson, P., Hosaka, K., Zhang, Y., Cao, R., Iwamoto, H., Yang, X., Nakamura, M., Wang, J., Zhuang, R., Morikawa, H., Xue, Y., Braun, H., Beyaert, R., Samani, N., Nakae, S., Hams, E., Dissing, S., Fallon, P. G., … Cao, Y. (2016). The PDGF-BB-SOX7 axis-modulated IL-33 in pericytes and stromal cells promotes metastasis through tumour-associated macrophages. Nature Communications, 7, 11385. https://doi.org/10.1038/ncomms11385

[96] Yi, S., Yan, Y., Jin, M., Bhattacharya, S.,

Wang, Y., Wu, Y., Yang, L., Gine, E., Clot, G., Chen, L., Yu, Y., Zou, D., Wang, J., Phan, A. T., Cui, R., Li, F., Sun, Q., Zhai, Q., Wang, T., … Wang, L. (2022). Genomic and transcriptomic profiling reveals distinct molecular subsets associated with outcomes in mantle cell lymphoma. The Journal of Clinical Investigation, 132(3), e153283. https://doi.org/10.1172/JCI153283

[97] Yim, I. S., & Laronde, D. M. (2024). Biomarkers of epithelial-mesenchymal transition: E-cadherin and beta-catenin in malignant transformation of oral lesions. Canadian Journal of Dental Hygiene: CJDH = Journal Canadien de l'hygiene Dentaire: JCHD, 58(2), 111–119.

[98] Zheng, Y., Wang, Z., Ding, X., Dong, Y., Zhang, W., Zhang, W., Zhong, Y., Gu, W., Wu, Y., & Song, X. (2018). Combined Erlotinib and PF-03084014 treatment contributes to synthetic lethality in head and neck squamous cell carcinoma. Cell Proliferation, 51(3), e12424. https://doi.org/10.1111/cpr.12424

[99] Zhong, X., He, X., Wang, Y., Hu, Z., Huang, H., Zhao, S., Wei, P., & Li, D. (2022). Warburg effect in colorectal cancer: The emerging roles in tumor microenvironment and therapeutic implications. Journal of Hematology & Oncology, 15(1), 160. https://doi.org/10.1186/s13045-022-01358-5

[100] Zhou, X., Liu, S., Cai, G., Kong, L., Zhang, T., Ren, Y., Wu, Y., Mei, M., Zhang, L., & Wang, X. (2015). Long Non Coding RNA MALAT1 Promotes Tumor Growth and Metastasis by inducing Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma. Scientific Reports, 5, 15972. https://doi.org/10.1038/srep15972