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Genomics in oral cancer: A systematic review

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Abstract---Background: The genetic factors play an essential role in the cell behavior and function in areas affected with cancer, identifying them could help faster risk detection and mitigation of cases that can be easily saved without much therapeutic intervention at the primary stage itself. This review aims to develop comprehensive evidence regarding genomics in oral cancer initiation, regulation, and progress/inhibition. Material and Methods: A systematic review was carried out of all the reported literature on genomics and proteomics as biomarkers from January 2015 to December 2021 across 3 different search engines- Medline/PubMed, Google Scholar and Scopus. There were 61 articles for the genetic components of oral cancer after following the PRISMA guidelines. Results: Among the 61 articles a number of genes were identified which showed either over or under expression in presence of cancer. All of the proteins showed a rise in their levels in cancer cases compared to healthy cohorts and premalignant cases. The levels of these proteins were also raised significantly in the premalignant cases compared to the healthy

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patients. Conclusion: A conclusion can be drawn that not all gene markers are raised; some show low expressions.

Keywords---Genomics, Oral Cancer, Biomarkers

Introduction

There is a need to consider genetic factors that regulate the invitation and progression of oral cancer.[1] It is imperative to imitate better tests for early detection and prompt treatment, especially among the high risk and vulnerable groups such as tobacco addicts and those with familial tendencies for cancer.[2–4] Genes play a crucial role in developing oral squamous cell carcinoma, especially in the tongue and the buccal mucosa.[5] These can predict oral cancer and assist in early diagnosis, especially in precancerous lesions and conditions.[6] The cancer cells undergo modifications and exhibit abnormal metastases, causing a rapid spread.[7] Interestingly reports state that the protein genomics is different phenotypically inside the tumor cells while it is different outside the cells in the tumor environment.[8] This review aims to collate genomics in oral cancer initiation, regulation, and progress/inhibition.

Methodology

The review was registered with OSF (https://osf.io/yrqz8). The key concepts for the literature search were- Genes in cancer, the familial pattern of inheritance, alteration, codon, miRNA, DNA strand alteration, DNA repair, remodelling, apoptosis, and metastasis/spread. Medline/PubMed, Scopus, Google Scholar were used for literature search. The search was completed, from January to February 2022. Only freely available full-text articles from January 2015 to December 2021 were included.

Results

A search of various databases yielded 61 unique articles (Figure 01).

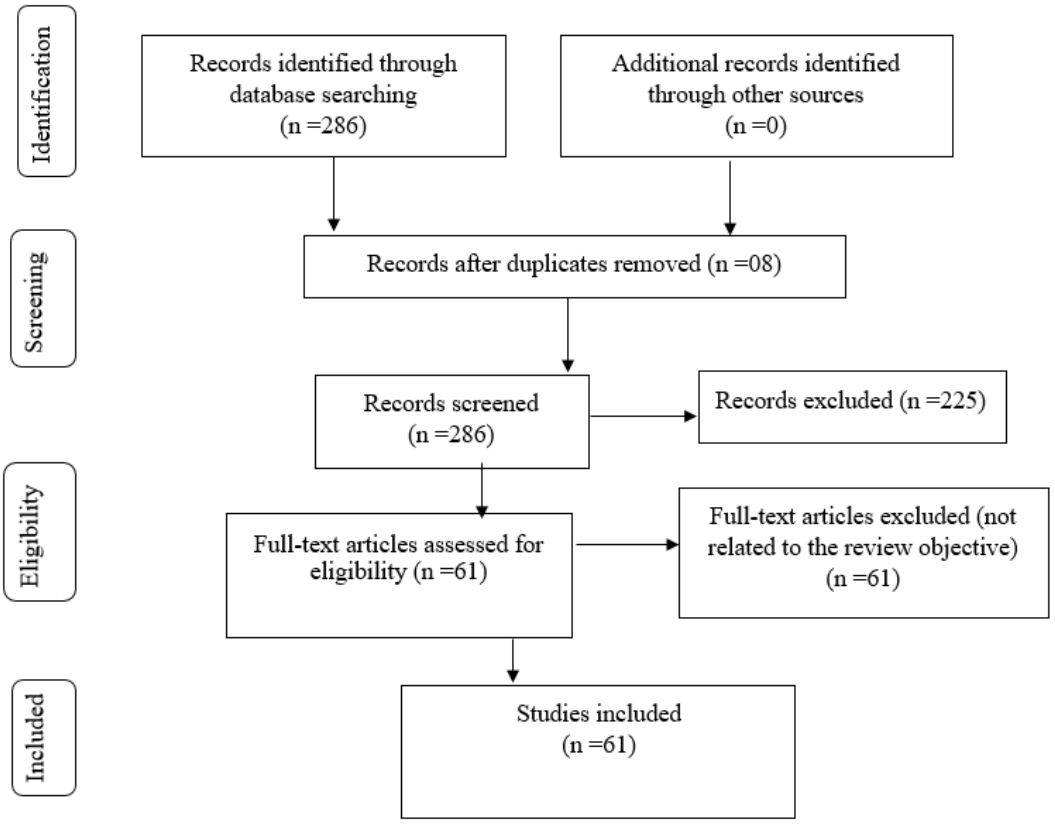

Figure 01: PRISMA flow chart:

There were 61 studies selected for the final analysis of the genomic composition of the review (Table 01), mostly the reports were based on Asian population.

Table 01: Study details on genomics as biomarkers

Author (year)	Sample size	Target Gene	Conclusion
Cao et al; China (2016) [9]	CAL-27, Tca8113, UM1 and UM2 OSCC cell lines	PDGFA	miR-375 inhibited cell migration and invasion by targeting the tumor promoter PDGF-A in UM1 cells
Lim et al; Korea (2017) [10]	YD-38 cell lines	SEMA6A	miR-203 induces apoptosis of YD-38 by targeting SEMA6A
Fang et al; China (2017) [11]	30 OSCC cases	UCA1, SF1	UCA1 levels upregulated in OSCC cells
Cai et al; China (2017) [12]	14 cases of tumor	PTPN11	MiR-186 expression inhibits cell growth; induces apoptosis through ERK and AKT pathways by targeting SHP2
Kawakubo-Yasukoch et al; Japan (2017) [13]	Tumor cell lines	CHD9, WRN	miR-200c-3p induces invasion
Zhang et al; China (2017) [14]	44 OSCC	IGF-1R	reduced miR-375 causes progression and poor survival
Rastogi et al; India (2017) [15]	20 OSCC	HDAC9	miR377 is downregulated in OSCC and suppresses through upregulation of HDAC9 and by inhibiting proapoptotic pathways via NR4A1/Nur77
Zhuang et al; China (2017) [86]	61 cases	PPP2R5A	inhibition of miR-218 improves cisplatin sensitivity
Zhuang et al; China (2017) [17]	110 OSCC patients	ΔNp63	increased ΔNp63 expression, reduced miR-138-5p expression has poor prognosis
Wang et al; China (2017) [18]	40 cases	HOXA9	miR-139-5p suppresses cell mobility by targeting HOXA9
Sun and Zhang; China (2017) [19]	Not specified	HK2	Restored HK2 expression in *miR-143* overexpressing cells exhibited oncogenic effects
Moon et al; Korea (2017)[20]	7 oral cancer cell lines and 2 immortalized human oral keratinocyte cell lines	miRNA	level of miR-145-5p predetermines sensitivity to photodynamic therapy
Wang et al; China (2017) [21]	40 OSCC	TRIM14	miR-195-5p with TRIM14 suppresses proliferation, migration, and invasion
Min et al; Korea (2017) [22]	_____	TRAF6	miR-146a-5p upregulation causes proliferation
Peng et al; Taiwan (2017); [23]	_____	miRNAs	miR-1 is novel bio signature in lymph node metastasis
He et al; China (2017) [24]	3 OSCC	COL1A1	miR-133a-3p inhibits the proliferation, migration through targeting COL1A1 and reducing expression
Shi et al; China	20 oral cancer and peri	NOX4	The interplay of miR-99a-5p and NOX4 affects OSCC cell

(2017) [25]	cancerous tissues		activities
Li et al; China (2017) [26]	6 OSCC cases	CCL2, IL-8	miR-124 is downregulated due to DNA hyper methylation
Shang et al; China (2017); [27]	21 OSCC cases	CDK4/6	down-regulation of CDK6 and Cyclin D1 in Tca8113 indicates ant proliferative function of miR-9
Tseng et al; Taiwan (2017) [28]	2 OSSC cases	Smad2	levels of miR-21-3p is associated with OSCC cell invasive ability
Peng et al; China (2018) [29]	OC3, FaDu, SCC25, HSC3, OECM1 and SAS cell lines	PDCD7	*miR-134* enhances OSCC progression by decreasing the expressions of PDCD7, E-cad
Kim et al; Korea (2018) [30]	68 OSCC cases	miR-155-5p	*miR-155-5p* associated with aggressive nature and rapid relapse of early-stage OSCC
Li et al; China (2018) [31]	20 OSCC samples	CAMK2N1	Down-regulation of miR-182-5p expression attenuates tumor growth, cell survival, and proliferation by regulation of the AKT/ERK1/2/NF-κB signaling pathways
Lien et al; Taiwan (2018) [32]	154 OSCC cases	CCL4	Higher levels of CCL4 expression is associated with advanced tumor status
Kim et al; Korea (2018) [33]	YD-38 cell line	BMI-1	*miR-203* is associated with suppression of Bmi-1
Nagai et al; Japan (2018) [34]	71 primary OSCC, 28 metastatic lymph node tissue	TIMP2	miR-205-5p directly regulates TIMP-2 expression, suppresses pro-MMP-2 activation by regulating TIMP-2 expression
Zheng et al; China (2018) [35]	86 OSCC cases	BIN1	Overexpression of BIN1 inhibits the proliferation, migration, and invasion ability
Li et al; China (2018) [36]	48 cases	RASSF5	miR-214 suppresses KB cell apoptosis through downregulation of RASSF5 expression and inhibition of FOXO3a phosphorylation, BIM expression
Wang et al ; China (2018); [37]	40 OSCC patients	DKK1	miR-1-3p suppresses the transit of SCC-4 cells from G0/G1 to S and induced apoptosis
Wang et al; China (2018) [38]	18 adult cases of OSCC	AKT3, BCL2L2	miR-16 inhibits cell proliferation and induced apoptosis through decreasing the downstream genes AKT3, BCL2L2
Li et al; China (2018) [39]	Lab Model	CD44-ROCK	miR-218-5p negatively regulates OSCC invasiveness by targeting the CD44–ROCK pathway
Lv et al; China (2018) [40]	23 OSCC cases	Notch1	miR-495 exerts an inhibitory effect through Notch1
Yuan et al; China (2018) [41]	20 OSCC tissues	RIG-I	negative association between RIG-I mRNA and miR-545 expression
Ningning ; China (2018) [42]	hTERT-OME, oral cancer cell lines	GFI1	expression of miR-650 is 6.5 folds more than normal cells
Feng et al; China	21 OSCC cases	NLRP3	miR-22 suppresses OSCC through NLRP3

(2018) [43]			
Lai et al; Taiwan (2018) [44]	3 human cell lines	ACOX1	miR-31-5p-ACOX1 axis constitute an oncogenic switch in cancer progression
Wang et al; China (2018) [45]	26 OSCC tissue pairs	MTDH	miR-655 overexpression suppresses cell proliferation and invasion by targeting MTDH and regulating the PTEN/AKT pathway
Lin et al; Taiwan (2018) [46]	70 OSCC cases	CCNG2	repression of CCNG2 by miR-1246 leads to elevated oncogenicity
Wei et al; China (2019) [47]	40 OSCC cases	SOX4	Overexpression of miR-199a-5p suppressed invasion and migration of OSCC cells by blocking SOX4/EMT pathway
Huang, Sing and Li; China (2019) [48]	SCC9 and the primary normal human oral keratinocyte cell linings	Smad2	miR-18a-5p upregulation promoted cell viability, migration and invasion of OSCC cells and inhibited cell apoptosis *in vitro* by activating the TGF-β1/Smad2 pathway
Mahmood et al; Pakistan (2019) [49]	100 samples	Smad2	serum miR-21 levels reflects tissue mir21 expression
Chen et al; China; (2019); [50]	52 OSCC cases	GLUT1	miRNA-10a is upstream activator of GLUT1
Chen et al; China (2019) [51]	134 OSCC samples	FGF2	miR-23a-3p is prognostic biomarker
Kurihara-Shimomura et al; Japan (2019) [52]	49 OSCC cases	CDH1	miR-29b-1-5p is an oncomiR
Kao et al; Japan (2019) [53]	43 OSCC cases	SIRT3	partial reversion of miR-31 driven phenotypic changes modulated by means of profound SIRT3 expression
Xie et al; China (2019) [54]	36 cases	COL10A1	secretion of hBMSCs inhibit COL10A1 and inhibit proliferation, invasion, and migration of oral cancer cells
Shi et al; China (2019) [55]	20 OSCC cases, 10 normal tissue	LIMK1	upregulation of miR-106a is inhibits proliferation
Chen et al; Taiwan (2019) [56]	OSCC cell lines	PRXL2A	miR-211-TCF12 oncogenic axis upregulates PRXL2A expression by transcriptional activation
Wang et al; China (2019) [57]	20 OSCC cases	CYP3A5	upregulation of miR-543 promotes cell proliferation, invasion and migration by inhibition of CYP3A5 expression
Zeng et al; China (2019) [58]	254 OSCC patients	YAP1	miR -138 is a prognostic biomarker for OSCC
Leong et al; China (2019) [59]	25 OSCC cases	RALBP1	Over expression of RLBP1 increases glucose uptake, aerobic glycolysis mediated ATP synthesis
Wu et al; China (2019) [60]	62 OSCC cases	ARID2	miR-155-5p-ARID2 axis regulated migration and invasion by facilitating EMT
Lihua et al; China	50 OSCC tissues	FBXW7	miR-223 expression is higher

(2019) [61]			
Lu et al; China (2019) [62]	157 OSCC tissues	GRAP	miR-654-5p targets GRAP
Chen et al; China (2019) [63]	70 OSCC tissues	CD36	miR-1254 is downregulated
Wei et al; China (2019) [64]	60 OSCC tissues	IKKβ	miR-199a-5p is as suppressor via the IKKβ, inhibits activation of the NF-κB pathway
Wei et al; China (2019) [65]	OSCC cell line	SCAI	inhibition of miR-5100 inhibits migration and invasion of TCA8113 cells via SCAI expression
Sun et al; China (2019) [66]	47 OSCC patients	miR-382-5p	CAF-derived exosomes transport miR-382-5p, contribute to migration and invasion
Hsing et al; Taiwan (2019) [67]	35 OSCC cases	TMEM182	upregulation of miR-450a reduces cellular adhesion to matrix by targeting TMEM182, enhances tumor invasion
Chao et al; Taiwan (2019) [68]	40 OSCC samples	DDR1	Aberrant methylation of *ANK1* causes epigenetic silencing of ANK1, miR-486-3p
He et al; China (2020) [69]	OSCC cell lines	IL32/AKT	miR-29b-3p suppresses the IL32/AKT signaling axis

Discussion

A previous systematic review has enumerated other genes; different to the ones in the present review. [70] OSCC from leukoplakia at an accuracy rate of 97.8%. Another study 7 genes with more than 95% rate of accuracy to differentiate between cases of mild dysplasia and hyperplasia from those who have higher grades of dysplasia and OSCC.[71] Various genes such as glycoprotein tenascin and osteopontin bring about the inhibition of the macrophage functions and help to enhance the survival of metastases in cases of squamous cell carcinoma. Arachidonate 5-lipoxygenase is the major enzyme-producing eicosanoid, which plays a role in the progression and metastasis. Overexpression of Stanniocalcin-1 in oral squamous cell carcinoma is associated with tumor aggression and poor prognosis. Other altered genes such as-laminin 5, moesin, and ezrin are associated with the invasiveness of oral cancer. These genes undergo interface with keratinocyte adhesion and are linked to the membrane-cytoskeletal. A varied array of genes are decreased in the expression in tumor progress. Keratins 4, 13, and 15 and occludin, that determines the structure, and genes that suppress the tumor as-BRUSH-1, MXI1, and oxidative stress response 1; lose their degree of expression in tumors.[70] There are a group of 102 epithelial predictor genes with predictiveness accuracy up to 100% for N0 status and 77% for N+ status, and overall accuracy of 86%. [70,71] They encode the components of the extracellular matrix that are involved in the adhesion of the cell. Nguyen et al. reported a panel of 8 genes that accurately predicts metastases.[72] PTHLH gene encodes the protein of the hormones of the parathyroid family.[32] CD9+ACTB and CD9+CD82 correlate with the metastasis of the cervical lymph node while CD151+GAPDH correlates with outcome of mortality. They adversely affects adhesion of cells, transduction of signals, proliferation, metastasis, cell differentiation, immunocytes activation, cell fertilization and viral infection. [73] The role of the other genes like *CDKN2A/p16, p16INK4A* and *p15INK4B* in cell cycle and senescence, *CDH1/E-cadherin* in cell adhesion, PTEN in differentiation, survival, proliferation, invasion, apoptosis; DAPK1 in apoptosis, MGMT and MLH1 in altered DNA repair, RARB2 in proliferation, RASSF1/2 in cell cycle, apoptosis, and microtubule formation; APC in cell proliferation, Survivin in proliferation and apoptosis, p14(ARF) and *RARβ* in cell proliferation, division, angiogenesis is well established.[74] CYP raised levels indicate a higher risk of squamous cell and metastasis.[57] A variant allele of CYP2A6 (rs28399433) is associated with a low risk for cancer.[70,74] rs1934951 is associated with a higher risk of oral cancer.[75] Decreased VEGF-C expression and lymphangiogenes is modulated by miRNA genes.[32] There is a difference in distribution of the vascular endothelial growth factor (VEGF) gene C/T polymorphism between healthy and oral cancer patients.[76] VEGF plays a role in the process of neovascularization as an angiogenic factor.[32] Tumor protein p53 studies were not recently reported, though it is a well-known genetic biomarker, associated with apoptosis and cell cycle control. [70] Mutation of the encoding p53 gene (TP53) and its higher concentration is associated with poor prognosis. These genes are missing with regards to the other forms of oral cancer apart from OSCC. The genetic biomarkers are neither single nor appear in group for specific form/stage of cancer. Genetic screening may help to understand the propensity towards cancer; its rate of progression or help to predict the mortality rates. The role of genes when other active factors are active is to be evaluated further. The cost factor, its

usefulness in cases of other oral inflammation along with cancer; associated co-morbidities and with low risk cases is to be reported across different groups. There is a lack of uniformity in reporting biomarkers in oral cancer. It is yet to be a regular practice to screen cases for genetic markers in practice.

Conclusion

Of the 61 articles selected for the gene biomarkers in oral cancer only a few were similar to the previous reports. The genes associated with oral cancer can serve as an adjunct to the clinical assessment and other diagnostic screening methods. The role of such genes when other factors are present and active is to be further evaluated.

References

1. Shah FD, Begum R, Vajaria BN, Patel KR, Patel JB, Shukla SN, et al. A review on salivary genomics and proteomics biomarkers in oral cancer. Indian J Clin Biochem. 2011;26: 326–34.
2. Public Health England. A report on incidence, survival and mortality rates of oral cancer in England. 2020.
3. GDC. Mouth cancer cases reach record high GDC publishes 2019 fitness to practise statistics. 2021.
4. Macpherson LMD. Raising awareness of oral cancer from a public and health professional perspective. Br Dent J. 2018;225: 809–814.
5. Carvalho K, Sawant P, Dhupar A, Spadigam A. A case of oral squamous cell carcinoma in a nontobacco habitué. Int J Appl Basic Med Res. 2017;7: 278.
6. Irani S. New insights into oral cancer—Risk factors and prevention: A review of literature. Int J Prev Med. 2020;11: 202.
7. Quadri MF, Tadakamadla S, John T. Smokeless tobacco and oral cancer in the Middle East and North Africa: A systematic review and meta-analysis. Tob Induc Dis. 2019;17.
8. Carnielli CM, Macedo CCS, De Rossi T, Granato DC, Rivera C, Domingues RR, et al. Combining discovery and targeted proteomics reveals a prognostic signature in oral cancer. Nat Commun. 2018;9.
9. Cao Z-H, Cheng J-L, Zhang Y, Bo C-X, Li Y-L. MicroRNA-375 inhibits oral squamous cell carcinoma cell migration and invasion by targeting platelet-derived growth factor-A. Mol Med Rep. 2017;15: 922–928.
10. Lim HS, Kim CS, Kim JS, Yu SK, Go DS, Lee SA, et al. Suppression of oral carcinoma oncogenic activity by microRNA-203 via down-regulation of SEMA6A. Anticancer Res. 2017;37: 5425–5433.
11. Fang Z, Zhao J, Xie W, Sun Q, Wang H, Qiao B. LncRNA UCA1 promotes proliferation and cisplatin resistance of oral squamous cell carcinoma by sunppressing miR-184 expression. Cancer Med. 2017;6: 2897–2908.
12. Cai Z, Hao X-Y, Liu F-X. MicroRNA-186 serves as a tumor suppressor in oral squamous cell carcinoma by negatively regulating the protein tyrosine phosphatase SHP2 expression. Arch Oral Biol. 2018;89: 20–25.
13. Kawakubo-Yasukochi T, Morioka M, Hazekawa M, Yasukochi A, Nishinakagawa T, Ono K, et al. miR-200c-3p spreads invasive capacity in human oral squamous cell carcinoma microenvironment. Mol Carcinog. 2018;57: 295–302.

14. Zhang B, Li Y, Hou D, Shi Q, Yang S, Li Q. MicroRNA-375 Inhibits Growth and Enhances Radiosensitivity in Oral Squamous Cell Carcinoma by Targeting Insulin Like Growth Factor 1 Receptor. Cell Physiol Biochem. 2017;42: 2105–2117.
15. Rastogi B, Kumar A, Raut SK, Panda NK, Rattan V, Joshi N, et al. Downregulation of miR-377 Promotes Oral Squamous Cell Carcinoma Growth and Migration by Targeting HDAC9. Cancer Invest. 2017;35: 152–162.
16. Zhuang Z, Hu F, Hu J, Wang C, Hou J, Yu Z, et al. MicroRNA-218 promotes cisplatin resistance in oral cancer via the PPP2R5A/Wnt signaling pathway. Oncol Rep. 2017;38: 2051–2061.
17. Zhuang Z, Xie N, Hu J, Yu P, Wang C, Hu X, et al. Interplay between ΔNp63 and miR-138-5p regulates growth, metastasis and stemness of oral squamous cell carcinoma. Oncotarget. 2017;8: 21954–21973.
18. Wang K, Jin J, Ma T, Zhai H. MiR-139-5p inhibits the tumorigenesis and progression of oral squamous carcinoma cells by targeting HOXA9. J Cell Mol Med. 2017;21: 3730–3740.
19. Sun X, Zhang L. MicroRNA-143 suppresses oral squamous cell carcinoma cell growth, invasion and glucose metabolism through targeting hexokinase 2. Biosci Rep. 2017;37.
20. Moon S, Kim DK, Kim J. Apoptosis-related microRNA-145-5p enhances the effects of pheophorbide a-based photodynamic therapy in oral cancer. Oncotarget. 2017;8: 35184–35192.
21. Wang T, Ren Y, Liu R, Ma J, Shi Y, Zhang L, et al. miR-195-5p Suppresses the Proliferation, Migration, and Invasion of Oral Squamous Cell Carcinoma by Targeting TRIM14. Biomed Res Int. 2017;2017: 1–13.
22. Min S-K, Jung SY, Kang HK, Park S-A, Lee JH, Kim M-J, et al. Functional diversity of miR-146a-5p and TRAF6 in normal and oral cancer cells. Int J Oncol. 2017;51: 1541–1552.
23. Peng C-Y, Liao Y-W, Lu M-Y, Yu C-H, Yu C-C, Chou M-Y. Downregulation of miR-1 enhances tumorigenicity and invasiveness in oral squamous cell carcinomas. J Formos Med Assoc. 2017;116: 782–789.
24. He B, Lin X, Tian F, Yu W, Qiao B. MiR-133a-3p Inhibits Oral Squamous Cell Carcinoma (OSCC) Proliferation and Invasion by Suppressing COL1A1. J Cell Biochem. 2018;119: 338–346.
25. Shi Y, Bo Z, Pang G, Qu X, Bao W, Yang L, et al. MiR-99a-5p regulates proliferation, migration and invasion abilities of human oral carcinoma cells by targeting NOX4. Neoplasma. 2017;64: 666–673.
26. Li X, Fan Q, Li J, Song J, Gu Y. MiR-124 down-regulation is critical for cancer associated fibroblasts-enhanced tumor growth of oral carcinoma. Exp Cell Res. 2017;351: 100–108.
27. Shang A, Lu W-Y, Yang M, Zhou C, Zhang H, Cai Z-X, et al. miR-9 induces cell arrest and apoptosis of oral squamous cell carcinoma via CDK 4/6 pathway. Artif Cells, Nanomedicine, Biotechnol. 2017; 1–9.
28. Tseng H, Tseng Y, You J, Kang B, Wang T, Yang C, et al. Next-generation Sequencing for microRNA Profiling: MicroRNA-21-3p Promotes Oral Cancer Metastasis. Anticancer Res. 2017;37: 1059–1066.
29. Peng S-Y, Tu H-F, Yang C-C, Wu C-H, Liu C-J, Chang K-W, et al. miR-134 targets PDCD7 to reduce E-cadherin expression and enhance oral cancer progression. Int J Cancer. 2018;143: 2892–2904.
30. KIM H, YANG JM, AHN S-H, JEONG W-J, CHUNG J-H, PAIK JH. Potential

Oncogenic Role and Prognostic Implication of MicroRNA-155-5p in Oral Squamous Cell Carcinoma. Anticancer Res. 2018;38: 5193–5200.
31. Li N, Nan C-C, Zhong X-Y, Weng J-Q, Fan H-D, Sun H-P, et al. miR-182-5p Promotes Growth in Oral Squamous Cell Carcinoma by Inhibiting CAMK2N1. Cell Physiol Biochem. 2018;49: 1329–1341.
32. Lien M-Y, Tsai H-C, Chang A-C, Tsai M-H, Hua C-H, Wang S-W, et al. Chemokine CCL4 Induces Vascular Endothelial Growth Factor C Expression and Lymphangiogenesis by miR-195-3p in Oral Squamous Cell Carcinoma. Front Immunol. 2018;9: 412.
33. KIM J-S, CHOI DW, KIM CS, YU S-K, KIM H-J, GO D-S, et al. MicroRNA-203 Induces Apoptosis by Targeting Bmi-1 in YD-38 Oral Cancer Cells. Anticancer Res. 2018;38: 3477–3485.
34. Nagai H, Hasegawa S, Uchida F, Terabe T, Ishibashi Kanno N, Kato K, et al. MicroRNA-205-5p suppresses the invasiveness of oral squamous cell carcinoma by inhibiting TIMP-2 expression. Int J Oncol. 2018;52: 841–850.
35. Zheng J, Wang J, Jia Y, Liu T, Duan Y, Liang X, et al. microRNA-211 promotes proliferation, migration, and invasion ability of oral squamous cell carcinoma cells via targeting the bridging integrator 1 protein. J Cell Biochem. 2019;120: 4644–4653.
36. Li TK, Yin K, Chen Z, Bao Y, Zhang SX. MiR-214 regulates oral cancer KB cell apoptosis through targeting RASSF5. Genet Mol Res. 2017;16.
37. Wang Z, Wang J, Chen Z, Wang K, Shi L. MicroRNA-1-3p inhibits the proliferation and migration of oral squamous cell carcinoma cells by targeting DKK1. Biochem Cell Biol. 2018;96: 355–364.
38. Wang X, Li G. MicroRNA-16 functions as a tumor-suppressor gene in oral squamous cell carcinoma by targeting AKT3 and BCL2L2. J Cell Physiol. 2018;233: 9447–9457.
39. Li X, He J, Shao M, Cui B, Peng F, Li J, et al. Downregulation of miR-218-5p promotes invasion of oral squamous cell carcinoma cells via activation of CD44-ROCK signaling. Biomed Pharmacother. 2018;106: 646–654.
40. Lv L, Wang Q, Yang Y, Ji H. MicroRNA-495 targets Notch1 to prohibit cell proliferation and invasion in oral squamous cell carcinoma. Mol Med Rep. 2018;19: 693–702.
41. Yuan G, Wu H, Du Y, He F. Tumor suppressor role of microRNA-545 in oral squamous cell carcinoma. Oncol Lett. 2018;17: 2063–2068.
42. Ningning S, Libo S, Chuanbin W, Haijiang S, Qing Z. MiR-650 regulates the proliferation, migration and invasion of human oral cancer by targeting growth factor independent 1 (Gfi1). Biochimie. 2019;156: 69–78.
43. Feng X, Luo Q, Wang H, Zhang H, Chen F. MicroRNA-22 suppresses cell proliferation, migration and invasion in oral squamous cell carcinoma by targeting NLRP3. J Cell Physiol. 2018;233: 6705–6713. 1
44. Lai Y-H, Liu H, Chiang W-F, Chen T-W, Chu LJ, Yu J-S, et al. MiR-31-5p-ACOX1 Axis Enhances Tumorigenic Fitness in Oral Squamous Cell Carcinoma Via the Promigratory Prostaglandin E2. Theranostics. 2018;8: 486–504.
45. Wang Q, Lv L, Li Y, Ji H. MicroRNA-655 suppresses cell proliferation and invasion in oral squamous cell carcinoma by directly targeting metadherin and regulating the PTEN/AKT pathway. Mol Med Rep. 2018;18: 3106–3114.
46. Lin S-S, Peng C-Y, Liao Y-W, Chou M-Y, Hsieh P-L, Yu C-C. miR-1246 Targets CCNG2 to Enhance Cancer Stemness and Chemoresistance in Oral

Carcinomas. Cancers (Basel). 2018;10: 272.
47. Wei D, Wang W, Shen B, Zhou Y, Yang X, Lu G, et al. MicroRNA-199a-5p suppresses migration and invasion in oral squamous cell carcinoma through inhibiting the EMT-related transcription factor SOX4. Int J Mol Med. 2019;44: 185–195.
48. Huang C, Song H, Lai L. The role and mechanism of microRNA-18a-5p in oral squamous cell carcinoma. Mol Med Rep. 2019;20: 1637–1644.
49. Mahmood N, Hanif M, Ahmed A, Jamal Q, Mushtaq S, Khan A, et al. Circulating miR-21 as a prognostic and predictive biomarker in oral squamous cell carcinoma. Pakistan J Med Sci. 2019;35: 1408–1412.
50. Chen Y, Song Y, Yu Y, Cheng W, Tong X. miRNA-10a promotes cancer cell proliferation in oral squamous cell carcinoma by upregulating GLUT1 and promoting glucose metabolism. Oncol Lett. 2019.
51. Chen F, Qi S, Zhang X, Wu J, Yang X, Wang R. miR-23a-3p suppresses cell proliferation in oral squamous cell carcinomas by targeting FGF2 and correlates with a better prognosis. Pathol - Res Pract. 2019;215: 660–667.
52. Kurihara-Shimomura M, Sasahira T, Shimomura H, Nakashima C, Kirita T. The Oncogenic Activity of miR-29b-1-5p Induces the Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma. J Clin Med. 2019;8: 273.
53. Kao Y-Y, Chou C-H, Yeh L-Y, Chen Y-F, Chang K-W, Liu C-J, et al. MicroRNA miR-31 targets SIRT3 to disrupt mitochondrial activity and increase oxidative stress in oral carcinoma. Cancer Lett. 2019;456: 40–48.
54. Xie C, Du L-Y, Guo F, Li X, Cheng B. Exosomes derived from microRNA-101-3p-overexpressing human bone marrow mesenchymal stem cells suppress oral cancer cell proliferation, invasion, and migration. Mol Cell Biochem. 2019;458: 11–26.
55. Shi B, Ma C, Liu G, Guo Y. MiR-106a directly targets LIMK1 to inhibit proliferation and EMT of oral carcinoma cells. Cell Mol Biol Lett. 2019;24: 1.
56. Chen Y-F, Wei Y-Y, Yang C-C, Liu C-J, Yeh L-Y, Chou C-H, et al. miR-125b suppresses oral oncogenicity by targeting the anti-oxidative gene PRXL2A. Redox Biol. 2019;22: 101140.
57. Wang L, Chen W, Zha J, Yan Y, Wei Y, Chen X, et al. miR-543 acts as a novel oncogene in oral squamous cell carcinoma by targeting CYP3A5. Oncol Rep. 2019;42: 973–990.
58. Zeng D, Xu H, Ji N, Li J, Zhou M, Dan H, et al. In situ measurement of miR-138 expression in oral squamous cell carcinoma tissue supports the role of this microRNA as a tumor suppressor. J Oral Pathol Med. 2019;48: 911–918.
59. Ieong C, Ma J, Lai W. RALBP1 regulates oral cancer cells via Akt and is a novel target of miR-148a-3p and miR-148b-3p. J Oral Pathol Med. 2019;48: 919–928.
60. Wu M, Duan Q, Liu X, Zhang P, Fu Y, Zhang Z, et al. MiR-155-5p promotes oral cancer progression by targeting chromatin remodeling gene ARID2. Biomed Pharmacother. 2020;122: 109696.
61. Jiang L, Lv L, Liu X, Jiang X, Yin Q, Hao Y, et al. MiR-223 promotes oral squamous cell carcinoma proliferation and migration by regulating FBXW7. Cancer Biomarkers. 2019;24: 325–334.
62. Lu M, Wang C, Chen W, Mao C, Wang J. miR-654-5p Targets GRAP to Promote Proliferation, Metastasis, and Chemoresistance of Oral Squamous Cell Carcinoma Through Ras/MAPK Signaling. DNA Cell Biol. 2018;37: 381–

388.
63. Chen R, Zhang Y, Zhang X. MiR-1254 Functions as a Tumor Suppressor in Oral Squamous Cell Carcinoma by Targeting CD36. Technol Cancer Res Treat. 2019;18: 153303381985944.
64. Wei D, Shen B, Wang W, Zhou Y, Yang X, Lu G, et al. MicroRNA-199a-5p functions as a tumor suppressor in oral squamous cell carcinoma via targeting the IKKβ/NF-κB signaling pathway. Int J Mol Med. 2019;43: 1585–1596.
65. Wei Z, Lyu B, Hou D, Liu X. Mir-5100 Mediates Proliferation, Migration and Invasion of Oral Squamous Cell Carcinoma Cells Via Targeting SCAI. J Investig Surg. 2021;34: 834–841.
66. Sun L, Xu K, Cui J, Yuan D, Zou B, Li J, et al. Cancer-associated fibroblast-derived exosomal miR-382-5p promotes the migration and invasion of oral squamous cell carcinoma. Oncol Rep. 2019;42: 1319–1328.
67. Hsing E-W, Shiah S-G, Peng H-Y, Chen Y-W, Chuu C-P, Hsiao J-R, et al. TNF-α-induced miR-450a mediates TMEM182 expression to promote oral squamous cell carcinoma motility. Ahmad A, editor. PLoS One. 2019;14: e0213463.
68. Chou S-T, Peng H-Y, Mo K-C, Hsu Y-M, Wu G-H, Hsiao J-R, et al. MicroRNA-486-3p functions as a tumor suppressor in oral cancer by targeting DDR1. J Exp Clin Cancer Res. 2019;38: 281.
69. He J, Ye W, Kou N, Chen K, Cui B, Zhang X, et al. MicroRNA-29b-3p suppresses oral squamous cell carcinoma cell migration and invasion via IL32/AKT signalling pathway. J Cell Mol Med. 2020;24: 841–849.
70. Kasradze D, Juodzbalys G, Guobis Z, Gervickas A, Cicciù M. Genetic and proteomic biomarkers of head-and-neck cancer: A systematic review. J Cancer Res Ther. 2020;16: 410.
71. Kondoh N, Ohkura S, Arai M, Hada A, Ishikawa T, Yamazaki Y, et al. Gene expression signatures that can discriminate oral leukoplakia subtypes and squamous cell carcinoma. Oral Oncol. 2007;43: 455–462.
72. Nguyen HB, Jaehne AK, Jayaprakash N, Semler MW, Hegab S, Yataco AC, et al. Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. Crit Care. 2016;20: 160.
73. Hirano C, Nagata M, Noman AA, Kitamura N, Ohnishi M, Ohyama T, et al. Tetraspanin gene expression levels as potential biomarkers for malignancy of gingival squamous cell carcinoma. Int J Cancer. 2009;124: 2911–2916.
74. Irimie A, Ciocan C, Gulei D, Mehterov N, Atanasov A, Dudea D, et al. Current Insights into Oral Cancer Epigenetics. Int J Mol Sci. 2018;19: 670.
75. Canova C, Hashibe M, Simonato L, Nelis M, Metspalu A, Lagiou P, et al. Genetic Associations of 115 Polymorphisms with Cancers of the Upper Aerodigestive Tract across 10 European Countries: The ARCAGE Project. Cancer Res. 2009;69: 2956–2965.
76. KU K, WAN L, PENG H, TSAI M, TSAI C, TSAI F. Vascular endothelial growth factor gene-460 C/T polymorphism is a biomarker for oral cancer. Oral Oncol. 2005;41: 497–502.