Editorial: Genetics and Molecular Mechanisms of Oral and Esophageal Squamous Cell Carcinoma

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Editorial on the Research Topic

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Oral squamous cell carcinoma (OSCC) is the most common histopathological type of oral cancer, with typical characteristics of low 5-year survival rate and poor prognosis (1, 2). Importantly, there are many factors affecting its occurrence and progression, in which genome alterations are critical indicators of the proper diagnosis and treatment (3). Carcinogenesis is a multi-step process, which involves the accumulation of genetic and epigenetic changes of oncogenes or tumor suppressor genes (4). Therefore, better understanding of the genetic and molecular disorders of the disease is the key to early diagnosis, appropriate treatment and improving the prognosis of patients.

Nowadays, cancer treatment is developed more towards personalized and targeted treatment. The most widely used treatment are targeted immunotherapy, which have significantly improved the 5-year survival rate of many types of cancer (5, 6). However, for OSCC patients, the only approved targeted therapy is a monoclonal antibody against epidermal growth factor receptor (EGFR), with the trade name ‘cetuximab’ (7). Recently, two immunotherapeutic agents, i.e., pembrolizumab and nivolumab, have been approved for OSCC (8, 9). Nevertheless, patients are widely resistant to the targeted therapy such as cetuximab combined with radiotherapy (10), and only less than 20% of OSCC patients receiving immunotherapy have achieved lasting remission (11). Therefore, it is necessary to implement different treatment schemes for patients based on their different gene mutations. Fortunately, the recent development of high throughput sequencing technologies, including whole genome sequencing and whole exome sequencing, make the detection of gene mutations in tumor tissues more sensitive and comprehensive so that the personalized cancer treatment becomes possible (12). This personalized treatment topic focused on the two genes EGFR and TP53 most commonly mutant in OSCC. In the following, we will demonstrate the rationale and the existing dilemma of targeted therapy of OSCC based on these two genes in the prospect of gene sequencing technology served for precision medicine.

It is reported that EGFR is overexpressed in more than 90% of OSCC patients and is involved in tumor cell invasion and metastasis (13). The activation of EGFR leads to the phosphorylation and activation of downstream signal transduction mediators and promotes tumor cell proliferation, survival, angiogenesis, invasion and adhesion (14). A variety of strategies to block EGFR function have been developed as personalized methods to inhibit tumor growth and metastasis, in which, cetuximab is the only targeted drug approved in OSCC. It has also been widely used and studied in
patients with locally advanced OSCC and patients with recurrent and or metastatic OSCC. However, mutations that activate EGFR kinase activity are relatively rare in OSCC (15). In addition, SRC is a nonreceptor tyrosine kinase. It is involved in regulating cell signal transduction downstream of a variety of receptors, including members of EGFR family, and in the regulation of cell proliferation, migration, adhesion and apoptosis (16). SRC kinase activity also enhances EGFR signal transduction (17). Therefore, SRC activity may promote resistance to EGFR targeted personalized therapy through independent activation or association with other receptors (17). Therefore, the determination of SRC kinase activity may be the key to predict the possible positive clinical response of targeted therapy.

Another important gene is TP53, which regulates cell cycle and apoptosis induced by DNA damage (18). Studies have shown that TP53 regulates the expression of forkhead box M1 (FOXM1) transcription factor and can directly bind and inactivate Aurora kinase A (AURKA) (19). FOXM1, an important cell cycle mediator, is a transcription factor downstream of EGFR/PI3K/AKT cascade and controls cell survival, apoptosis, migration and angiogenesis (20). In addition, AURKA and AURKB are two cell cycle regulators controlled by FOXM1 (21). AURKA and AURKB both control the structure and function of cytoskeleton and chromosome and contribute to tumor progression, metastasis and diffusion (22). EGFR signaling pathway can improve the translation and transcription efficiency of AURKA and induce the overexpression of AURKA (23). As an important cell cycle regulator, Aurora kinase is a reliable target in a variety of malignant tumors. At present, several Aurora kinase inhibitors have been developed (24, 25). In preclinical evaluation studies, it was found that AURKA and AURKB inhibitors ENMD2076 and AZD1152, as well as pan Aurora agents such as AMG900, can induce growth arrest and apoptosis (26, 27). In a phase I/II study, laser kinase inhibitors were evaluated as a single drug for a variety of solid tumors including OSCC. However, only 3 of 20 OSCC patients receiving AMG900 had partial remission. This low success rate suggests that the overall the personalized intervention needs to be improved at the patient population, and meanwhile those patients who are more sensitive to Aurora kinase inhibitors also need to have further investigator e.g., identify the biomarkers they may share to indicate the efficacy of these compounds, so as to achieve better clinical results from this target therapy.

As a summary, one of the ultimate goals of cancer research is to better understand the disease-related biological process to identify the predictive biomarkers, which runs through the whole process of patient diagnosis, prognosis and treatment. The effect of clinical treatment often depends on the existence of specific cell targets. Despite the complexity of cancer genetics, tumor heterogeneity and drug resistance are still the difficulties of targeted therapy. However, the development of genomics related technologies, including whole genome sequencing and whole exome sequencing, has had a far-reaching impact on the personalized diagnosis and treatment of cancer patients (28).

**AUTHOR CONTRIBUTIONS**

BQ and SL wrote the manuscript. DWa and DWu made the draft revision. All authors contributed to the article and approved the submitted version.

**REFERENCES**

1. Hedberg ML, Goh G, Chiosea SI. Genetic Landscape of Metastatic and Recurrent Head and Neck Squamous Cell Carcinoma. J Clin Invest (2016) 126(4):1606. doi: 10.1172/JCI86862
2. Lee YS, Johnson DE, Grandis JR. An Update: Emerging Drugs to Treat Squamous Cell Carcinomas of the Head and Neck. Expert Opin Emerg Drugs (2018) 23(4):283–99. doi: 10.1080/1478728X.2018.1543400
3. Wang Y, Ow TJ, Myers JN. Pathways for Cervical Metastasis in Malignant Neoplasms of the Head and Neck Region. Clin Aniat (2012) 25(1):54–71. doi: 10.1002/ca.21249
4. Chow LQM. Head and Neck Cancer. N Engl J Med (2020) 382(1):60–72. doi: 10.1056/NEJMra1715715
5. Ferris RL. Immunology and Immunotherapy of Head and Neck Cancer. J Clin Oncol (2015) 33(29):3293–304. doi: 10.1200/JCO.2015.61.1509
6. Yarchoo M, Hopkins A, Jaffes EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med (2017) 377(25):2500–1. doi: 10.1056/NEJMct1713444
7. Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F, et al. Open-Label, Uncontrolled, Multicenter Phase II Study to Evaluate the Efficacy and Toxicity of Cetuximab as a Single Agent in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Failed to Respond to Platinum-Based Therapy. J Clin Oncol (2007) 25(16):2171–7. doi: 10.1200/JCO.2006.06.7447
8. De Felice F, Musio D, Tombolini V. Immune Check-Point Inhibitors and Standard Chemoradiotherapy in Definitive Head and Neck Cancer Treatment. J Pers Med (2021) 11(5):393. doi: 10.3390/jpm11050393
9. Chow LQM, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol (2016) 34(32):3838–45. doi: 10.1200/JCO.2016.68.1478
10. Machiels JP, Schmitt S. Molecular-Targeted Therapy of Head and Neck Squamous Cell Carcinoma: Beyond Cetuximab-Based Therapy. Curr Opin Oncol (2011) 23(3):241–8. doi: 10.1097/CCO.0b013e32834f581
11. Wang Z, Goto Y, Allevato MM, Wu VH, Saddawi-Konefka R, Giglardi M, et al. Disruption of the HER3-PI3K-mTOR Oncogenic Signaling Axis and PD-1 Blockade as a Multimodal Precision Immunotherapy in Head and Neck Cancer. Nat Commun (2021) 12(1):2383. doi: 10.1038/s41467-021-22619-w
12. Kim DH, Kim YS, Son NI, Kang CK, Kim AR. Recent Omics Technologies and Their Emerging Applications for Personalised Medicine. IET Syst Biol (2017) 11(3):87–98. doi: 10.1049/iet-syb.2016.0016
13. Pysrri A, Yu Z, Weinberger PM, Sasaki C, Haffty B, Camp R, et al. Quantitative Determination of Nuclear and Cytoplasmic Epidermal Growth Factor Receptor Expression in Oropharyngeal Squamous Cell Cancer by Using Automated Quantitative Analysis. Clin Cancer Res (2005) 11(16):5856–62. doi: 10.1158/1078-0432.CCR-05-0420
14. Rubin Grandis J, Zeng Q, Dening SD. Epidermal Growth Factor Receptor-Mediated Stat3 Signaling Blocks Apoptosis in Head and Neck Cancer. Laryngoscope (2000) 110(5):686–74. doi: 10.1097/00005553-200005000-00016
15. Lee JW, Soung YH, Kim SY, Kwon HW. Somatic Mutations of EGFR Gene in Squamous Cell Carcinoma of the Head and Neck. Clin Cancer Res (2005) 11(8):2879–82. doi: 10.1158/1078-0432.CCR-04-2029
16. Frame MC. Newest Findings on the Oldest Oncogene: How Activated Src Does it. J Cell Sci (2004) 117(7):989–98. doi: 10.1242/jcs.01111
17. Maa MC, Leu TH, McCellery DJ, Schatzman RC, Parsons SJ. Potentiation of Epidermal Growth Factor Receptor-Mediated Oncogenesis by C-Src.
Implications for the Etiology of Multiple Human Cancers. *Proc Natl Acad Sci USA* (1995) 92(15):6981–5. doi: 10.1073/pnas.92.15.6981

18. Wang S, Zhang Y, Huang J, Wong CC, Zhai J, Li C, et al. TRIM67 Activates P53 to Suppress Colorectal Cancer Initiation and Progression. *Cancer Res* (2019) 79(16):4086–98. doi: 10.1158/0008-5472.CAN-18-3614

19. Chen SS, Chang PC, Cheng YW, Tang FM, Lin YS. Suppression of the STK15 Oncogenic Activity Requires a Transactivation-Independent P53 Function. *EMBO J* (2002) 21(17):4491–9. doi: 10.1093/emboj/cdf409

20. Halasi M, Gartel AL. FOX(M1) News–It Is Cancer. *Mol Cancer Ther* (2013) 12(3):245–54. doi: 10.1158/1535-7163.MCT-12-0712

21. Yang N, Wang C, Wang Z, Zona S, Lin S-X, Wang X, et al. FOXM1 Recruits Nuclear Aurora Kinase A to Participate in a Positive Feedback Loop Essential for the Self-Renewal of Breast Cancer Stem Cells. *Oncogene* (2017) 36(24):3428–40. doi: 10.1038/onc.2016.490

22. Wang IC, Chen YJ, Hughes D, Petrovic V, Major ML, Park HJ, et al. Forkhead Box M1 Regulates the Transcriptional Network of Genes Essential for Mitotic Progression and Genes Encoding the SCF (Skp2-Cks1) Ubiquitin Ligase. *Mol Cell Biol* (2005) 25(24):10875–94. doi: 10.1128/MCB.25.24.10875-10894.2005

23. Hung LY, Tseng JT, Lee YC, Xia W, Wang Y-N, Wu M-L, et al. Nuclear Epidermal Growth Factor Receptor (EGFR) Interacts With Signal Transducer and Activator of Transcription 5 (STAT5) in Activating Aurora-A Gene Expression. *Nucleic Acids Res* (2008) 36(13):4337–51. doi: 10.1093/nar/gkn417

24. Tatsuka M, Yu Z, Weinberger PM, Sasaki C, Haffly B, Camp R, et al. Overexpression of Aurora-A Potentiates HRAS-Mediated Oncogenic Transformation and is Implicated in Oral Carcinogenesis. *Oncogene* (2005) 24(6):1122–7. doi: 10.1038/sj.onc.1208293

25. Pannone G, Hindi SA, Santoro A, Sanguegaldolce F, Rubini C, Cincione RI, et al. Aurora B Expression as a Prognostic Indicator and Possible Therapeutic Target in Oral Squamous Cell Carcinoma. *Int J Immunopathol Pharmacol* (2011) 24(1):79–88. doi: 10.1177/039463201102400110

26. Fletcher GC, Brokx RD, Denny TA, Hembrough TA, Plum SM, Fogler WE, et al. ENMD-2076 Is An Orally Active Kinase Inhibitor With Antiangiogenic and Antiproliferative Mechanisms of Action. *Mol Cancer Ther* (2011) 10(1):126–37. doi: 10.1158/1535-7163.MCT-10-0574

27. Payton M, Cheung HK, Ninniri MSS, Marinaccio C, Wayne WC, Hanestad K, et al. Dual Targeting of Aurora Kinases With AMG 900 Exhibits Potent Preclinical Activity Against Acute Myeloid Leukemia With Distinct Post-Mitotic Outcomes. *Mol Cancer Ther* (2018) 17(12):2575–85. doi: 10.1158/1535-7163.MCT-18-1086

28. Biankin AV, Hudson TJ. Somatic Variation and Cancer: Therapies Lost in the Mix. *Hum Genet* (2011) 130(1):79–91. doi: 10.1007/s00439-011-1010-0

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