Molecular Biology and Immunology of Head and Neck Cancer

Theresa Guo, MD*, Joseph A. Califano, MD

KEYWORDS

• Molecular biology • Targeted therapy • Immunology • Head and neck cancer

KEY POINTS

- Most head and neck squamous cell carcinomas are associated with smoking and alcohol, but an emerging subset of tumors is associated with human papillomavirus. These patients have improved clinical outcomes and a distinct genetic profile.
- Genetic sequencing of head and neck cancer revealed mutations in key cancer pathways, including p53, epidermal growth factor receptor (EGFR)/Ras/phosphatidylinositol 3-kinase (PI3K), Notch and apopototic pathways.
- Therapies targeted toward these pathways are limited but under investigation.
- Head and neck cancers may progress by immune evasion, which is another potential targetable mechanism under investigation.

In recent years, our knowledge and understanding of head and neck squamous cell carcinoma (HNSCC) has expanded dramatically. New high-throughput sequencing technologies have accelerated these discoveries since the first reports of whole-exome sequencing of HNSCC tumors in 2011.[1,2] In addition, the discovery of human papillomavirus (HPV) in relationship with oropharyngeal squamous cell carcinoma (SCC) has shifted our molecular understanding of the disease.[3] New investigation into the role of immune evasion in HNSCC has also led to potential novel therapies based on immune-specific systemic therapies.

DISTINCT ETIOLOGIC SUBSETS OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

HNSCC forms after accumulation of genetic events, which are accelerated by genomic instability related to carcinogen exposures, particularly tobacco and alcohol. These tumors may occur throughout the upper aerodigestive tract (oral cavity, oropharynx, larynx) and are found in older patients, usually with history of smoking

Department of Otolaryngology, Head and Neck Surgery, Johns Hopkins Medical Institutions, 1550 Orleans St, Baltimore, MD 21231, USA
* Corresponding author. Cancer Research Building CRB II, 5M, 1550 Orleans Street, Baltimore, MD 21231.
E-mail address: tguo5@jhmi.edu

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or alcohol use. They are also associated with p53 mutations and poor clinical outcomes, with 5-year survival of 33.8% to 66.8%, depending on subsite.[4,5]

Recently, HPV has been associated with a subset of HNSCC, chiefly in the oropharynx and primarily in younger, white, nonsmokers.[3,6] HPV is a double-stranded DNA virus that infects the squamous epithelium. High-risk subtypes, particularly HPV-16 and HPV-18, are associated with development of malignancy in both HNSCC and cervical cancer. The mechanism of oncogenesis is attributed to viral proteins E6 (which binds and degrades p53) and E7 (which inhibits retinoblastoma protein, a tumor suppressor gene that inhibits cell cycle progression).[7,8] Patients with HPV-related HNSCC have improved prognosis with longer overall survival, decreased rate of recurrence, and improved response to chemoradiation.[3,9]

GENETIC ALTERATIONS

In 2011, the first whole-exome sequencing of HNSCC was published.[1,2] Recently, the Cancer Genome Atlas (TCGA) Research Network performed integrated genomic analysis, including genome sequencing, copy number and loss of heterozygosity arrays, whole-genome methylation, and RNA sequencing on 279 head and neck cancers, constituting the largest cohort of sequenced tumors studied.[10]

Gene mutations were segregated by HPV tumor status. HPV-positive tumors harbored fewer mutations compared with HPV-negative tumors.[1,10,11] TP53 mutations were found almost exclusively in HPV-negative tumors,[1,10] whereas activating mutations and amplifications of PIK3CA (phosphatidylinositol 3-kinase, catalytic subunit alpha) were commonly seen in HPV-positive tumors (**Fig. 1**).[10] This finding is consistent with prior data showing the same distinct genetic alterations.[12]

Beyond sequencing, gene promoter methylation of several genes, including CDKN2A (cyclin-dependent kinase inhibitor 2A), CDH1 (cadherin 1 type 1, E-cadeherin), MGMT (O-6-methylguanine-DNA methyltransferase), and DAPK1 (death-associated protein kinase 1), has been established in oral SCC.[13] CDKN2A, a tumor suppressor gene, is one of the first genes in HNSCC to be associated with promoter methylation as a mechanism of downregulation.[14]

MAJOR PATHWAYS

TP53 and CDKN2A

The TP53 (tumor protein p53) gene encodes for the p53 protein, "guardian of the genome."[15] TP53 is one of the most frequently mutated genes in HNSCC[1,2,10,15] tumors and even premalignant lesions.[16] The p53 protein acts as a tumor suppressor that accumulates in response to stress, including DNA damage.[17] Accumulation of p53 induces cell cycle arrest to allow the cell to perform DNA repair. If damage is beyond repair, p53 induces apoptosis.[15] The expression of p53 is regulated by MDM2 (MDM2 proto-oncogene, E3 ubiquitin protein ligase), which inactivates and degrades p53.[18] The CDKN2A locus at 9p21 codes for 2 alternatively spliced proteins p14ARF and p16INK4A, which both regulate p53 function (**Fig. 2**).[19]

Most p53 mutations in HNSCC (50%–63%) are missense mutations.[1,2] Missense mutations in p53 can result in a stable protein with loss of key binding function or even act in a dominant negative fashion inactivating any remaining wild-type p53.[15] Tobacco exposure is associated with increased rates of TP53 mutations.[4,20] Mutations in TP53 have been associated with decreased overall survival,[21] increased locoregional recurrence rates,[22] and decreased response to therapy.[23,24]

In recent sequencing data, it was found that CDKN2A was mutated in 9% to 12% of tumors.[1,2] Loss of heterozygosity is frequently seen at the CDKN2A locus in HNSCC,