Molecular Aspects of Head and Neck Cancer Therapy

Sidharth V. Puram, MD, PhD[a,b], James W. Rocco, MD, PhD[c,*]

KEYWORDS

• Head and neck cancer • Squamous cell carcinoma • Molecular biology
• Targeted therapy • Synthetic lethality • Genomic sequencing
• Intratumor heterogeneity

KEY POINTS

- Head and neck squamous cell carcinoma (HNSCC) is driven by numerous mutations, with human papilloma virus negative (HPV–) cancers caused by more traditional risk factors (tobacco use/alcohol) tending to harbor more mutations, greater intratumor heterogeneity, and extensive copy number variation.
- Recent genomic insights suggest that targeted therapy of HNSCC will remain a significant challenge. Most mutations identified based on sequencing analyses are loss-of-function mutations in known and putative tumor suppressor genes that may require novel approaches, such as synthetic lethality.
- Oncogenic drivers are few and far between and often are present at low mutant allele frequencies, suggesting they may be poor choices for targeted therapy.
- One exception for targeted therapy may be activating Ras or PI3K mutations that occur at high frequency in HPV+ cancers, offering a potential avenue for therapy that may facilitate deintensification of chemoradiation therapy.
- Identification of genes implicated in tumor-immune interactions as well as loss of function mutations suggest that immunotherapy and modulation of immune surveillance may be a valuable therapeutic approach, supporting ongoing immunotherapy clinical trials.

INTRODUCTION

Despite advances in our understanding of tumor biology, including its evolutionary refinements, as well as radiation, chemotherapy, and surgical treatments,

Disclosures/Conflict of Interest: The authors have nothing to disclose.

[a] Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114, USA; [b] Department of Otology and Laryngology, Harvard Medical School, 25 Shattuck St., Boston, MA 02115, USA; [c] Department of Otolaryngology-Head and Neck Surgery, Wexner Medical Center, James Cancer Hospital, Solove Research Institute, The Ohio State University, 320 West 10th Avenue, Columbus, OH 43210, USA
* Corresponding author.
E-mail address: james.rocco@osumc.edu

Hematol Oncol Clin N Am 29 (2015) 971–992
http://dx.doi.org/10.1016/j.hoc.2015.07.003 **hemonc.theclinics.com**
0889-8588/15/$ – see front matter

head and neck squamous cell carcinoma (HNSCC) remains the sixth leading cause of cancer-related morbidity and mortality, with 550,000 new cases diagnosed each year.[1,2] These tumors arise from mucosal epithelium in the oral cavity, oropharynx, larynx, and hypopharynx, which together represent 75% of diagnosed cancers.[3]

HNSCC tumors can be broadly divided into those that are human papilloma virus (HPV)-negative (HPV–) and associated with alcohol and tobacco consumption,[4] and those that are HPV-positive (HPV+) and due to HPV infection primarily with serotype 16.[5,6] Although HPV– cancers arise via field cancerization and clonal progression in the setting of repetitive carcinogen application, HPV+ tumors harbor few mutations and are driven by a fundamentally distinct pathophysiologic mechanisms that rely on E6 and E7 viral proteins to inactivate or bypass cellular tumor suppressive responses.[7] Although recent vaccines against HPV (Gardasil, Cervarix) will influence the prevalence of HPV+ HNSCC in the decades to follow, for now, the incidence of HPV+ HNSCC continues to rise. Current estimates suggest that 45% to 90% of oropharyngeal squamous cell carcinomas (OPSCCs) are HPV+ with 90% associated with HPV serotype 16.[8,9] The division of HNSCC into two fundamentally distinct tumor cohorts with widely disparate survival rates based on HPV status represents one of the most significant developments of the past decade in head and neck cancer research and treatment.

Treatment for HNSCC is most often chosen based on the primary tumor subsite, TNM staging, and predicted functional outcomes following different treatment modalities. In general, early-stage (I or II) HNSCC is treated with local therapy, taking advantage of the ability of surgical removal or radiation to offer a curative modality. Advanced disease (stage III or IV) requires multimodality treatment with surgery, radiation, and/or chemotherapy.[10] Although the influence of treatment-related medical complications on mortality has declined,[11] and some improvements in head and neck survival have been documented, these are largely related to the increasing incidence of HPV+ cancers rather than substantive gain in the clinical management of HNSCC. Treatment failure in HNSCC relates to resistance of tumor cells to primary or adjuvant chemoradiation therapy, as well as residual undetectable microscopic disease that remains after surgical resection.

Recent whole-exome sequencing of HNSCC offers several lessons into how these tumors will need to be treated to improve on traditional therapeutic modalities. First, the sequencing of such a large number of tumors from numerous institutions demonstrates the successful endeavor of a multi-institutional collaborative effort to molecularly characterize the biology of head and neck tumors. Second, these analyses have validated that p53 inactivating mutations remain the predominant genetic defect identified, substantiating previous studies and emphasizing the observation that most tumors harbor loss-of-function mutations. Third, sequencing data separates HPV+ and HPV– tumors into distinct groups with completely different mutational profiles. Fourth, we have learned that HNSCC will be challenging to treat: there is no singular target for these tumors. Intratumor heterogeneity will also remain a challenge as we attempt to advance our therapeutic approaches.

In this review, we briefly discuss the molecular pathways driving HNSCC as identified using traditional genetics and biochemistry, but focus primarily on the new and interesting scientific advances in the field. In particular, we emphasize insights from recent whole-exome sequencing analyses of HNSCC, discuss lessons learned from analyses of intratumor heterogeneity, and explore the implications of recent studies on future therapeutic approaches.