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Therapeutic insights from genomic studies of head and neck squamous cell carcinomas

Peter S. Hammerman[1,2], **D. Neil Hayes**[3], and **Jennifer R. Grandis**[4,5]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

[2]Cancer Program, Broad Institute of Harvard and MIT, Cambridge, Massachusetts

[3]Department of Hematology/Oncology, University of North Carolina Lineberger Cancer Center, Chapel Hill, North Carolina

[4]Department of Otolaryngology, University of Pittsburgh and University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania

[5]Department of Pharmacology & Chemical Biology, University of Pittsburgh, Pittsburgh, Pennsylvania

Abstract

Large and comprehensive genomic surveys of head and neck squamous cell carcinomas are now greatly increasing our understanding of the diversity of this disease and the key genomic changes, which drive these tumors. The results from these studies are beginning to inform the introduction of novel therapies for patients with head and neck squamous cell cancers. Here, we review some of the key findings from recent genomic studies of head and neck cancers including the most comprehensive study to date from The Cancer Genome Atlas Network.

Keywords

Head and neck cancer; therapeutic biomarkers; cancer genomics

Introduction

Head and neck squamous cell carcinomas (HNSCC) are the fifth most common malignancy world-wide and comprise a diverse set of cancers arising in the upper aerodigestive tract mucosa(1). Unlike many other epithelial cancers, the majority of HNSCCs present at a locally advanced stage with cervical lymph node metastases. Over 90% of patients are treated with curative intent using a combination of surgery, radiation therapy and chemotherapy(2). To date, treatment approaches have been dictated by the anatomic site of the primary tumor with oral cavity cancers treated primarily with surgical resection and pharyngeal and laryngeal tumors with chemoradiation(3). While over one-half of patients

Correspondence to: Dr. Jennifer R. Grandis, W912 Biomedical Science Tower, 200 Lothrop Street, Pittsburgh, Pennsylvania 15213, Phone: 412-383-5405, grandisjr@upmc.edu.

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are cured with initial therapy, these treatments are highly morbid, and therapeutic options for individuals who relapse following initial treatment are limited(4). In the absence of information regarding the biologic underpinnings of individual tumors, predictive biomarkers have been lacking to guide therapy in both the initial treatment setting and in the treatment of relapsed/refractory disease. Establishing robust therapeutic biomarkers in HNSCCs has been challenging for several reasons including the heterogeneity of these tumors which display diversity in terms of their anatomy, clinical characteristics and in their association with conventional risk factors such as tobacco and alcohol exposure as well as with infection with the oncogenic Human Papilloma Virus (HPV) and Epstein-Barr Virus (EBV)(2, 5). Recent large-scale genomic profiling studies, notably that of The Cancer Genome Atlas (TCGA), have shed light on the molecular underpinnings of the diversity of HNSCCs. We highlight some of the key insights from this and other studies and the implications of these findings on our understanding of HNSCCs and therapeutic approaches.

The Genomic Landscape of non-HPV Driven HNSCCs

Despite advances in surgical approaches, radiotherapy and chemotherapies, treatment outcomes for patients with HNSCCs associated with the traditional risk factors of tobacco use, alcohol exposure, or both, remain disappointing as compared to patients with HPV-driven disease(5, 6). This clinical challenge has stimulated genomic studies focusing on this high-risk group of patients with the goal of identifying molecular aberrations, which could be targeted to improve clinical outcomes. However, at this time there are no agents in clinical use in HNSCCs that show enhanced activity associated with a genetic biomarker. While *EGFR* is overexpressed in HNSCC and has been shown to be associated with reduced survival, EGFR-directed therapies have not been especially efficacious(7, 8). Cetuximab, a monoclonal antibody directed against EGFR, is the only FDA approved targeted molecularly targeted agent for HNSCC, but response rates to this agent given as monotherapy are approximately 10% and it remains unclear how to predict the subset of patients most likely to respond to cetuximab or other EGFR-directed therapies despite a large number of studies addressing this topic(7, 9, 10).

Next-generation sequencing studies of non-HPV driven HNSCCs, including the TCGA project which characterized nearly 250 of these individuals (TCGA Network, *Nature*, in press), has demonstrated a complex landscape of alterations in gene expression, DNA copy number, somatic mutations, gene rearrangements and gene promoter methylation(11–15). These tumors are characterized by near-universal loss of *TP53* and *CKDN2A/RB1* by truncating mutation, deletion and/or alternative splicing. A summary of somatic alterations in genes regulating a number of key cellular pathways in HPV-negative and HPV-positive HNSCCs is presented in Table 1.

Of note, HPV-negative HNSCCs most closely resemble lung squamous cell carcinomas in terms of their spectra of genomic alterations and contain statistically enriched mutations and copy number alterations in genes regulating many of the same pathways in addition to widespread loss of both *TP53* and *CDKN2A/RB1*(16). These include regulation of squamous differentiation (*NOTCH1*, *RIPK4*, *IRF6*, *TP63*), oxidative stress (*NFE2L2*, *KEAP1*), WNT signaling (*AJUBA*, *FAT1*), immune evasion (*HLA-A*, *B2M*, *TGFBR2*) and chromatin

remodeling (*MLL2, NSD1*)(15) (TCGA Network, *Nature*, in press). While twenty percent of HPV-negative HNSCCs in the TCGA cohort displayed amplifications of Receptor Tyrosine Kinase (RTK) genes such as *EGFR, ERBB2, MET* and *FGFR1,* there were no recurrent mutations or fusions in RTK genes which have been associated with dramatic responses to small molecule kinase inhibitors in other tumor types such as lung adenocarcinoma. One possible exception is oncogenic exon 14 skipping in *MET,* which was reported in two HNSCC cases by TCGA and is found in 4–5% of lung adenocarcinoma and which may be associated with sensitivity to MET small molecule inhibitors.

Mutually exclusive mutations in RAS family genes, notably *RHOA, KRAS* and *HRAS,* are present but infrequently found in HNSCC (6% of TCGA cases), though recurrent mutations in *RHOA* at amino acid position 40 are worth noting; however, the biological significance of these *RHOA* mutations is unclear. Amplification of chromosome 3q, a region containing the *TP63, SOX2* and *PIK3CA* genes, is seen in the majority of both HPV-negative and HPV-positive HNSCCs and *PIK3CA* mutations are commonly found in both HPV-negative and HPV-positive disease, in agreement with prior studies(11, 14, 15, 17).

HPV-negative HNSCCs arise from a number of anatomic sites including the larynx, oral cavity and oropharynx and generally occur in the setting of heavy alcohol and/or tobacco exposure or, less commonly, in patients without these well-established risk factors. The TCGA cohort did not identify any mutated genes specific to an anatomic site, though the numbers of cases in each of these categories was insufficient to comprehensively address this question. It should be noted that a prior report suggested *TERT* promoter mutations are enriched in tongue cancers(18). In contrast to lung cancers in which many targetable genomic alterations have been identified specifically in patients who lack exogeneous carcinogen exposure in the form of tobacco, two small studies of HNSCCs arising in HPV-negative individuals with minimal tobacco or alcohol histories did not identify any recurrent kinase alterations(19, 20).

HPV-negative HNSCCs demonstrate clear evidence of molecular diversity, as suggested by expression profiling studies which clearly demonstrate diverse biologic subclasses within HPV-negative disease including a class of tumors without *EGFR* amplification and/or overexpression, previously termed “atypical” HNSCCs, which consist of approximately 20% of HPV-negative cases and the vast majority of HPV-positive HNSCCs(21, 22). An intriguing mutational pattern identified by TCGA was a subset of HPV-negative HNSCCs originating in the oral cavity with few to no copy number alterations was statistically enriched for *HRAS, CASP8* and *PIK3CA* mutations and lack of *TP53* mutation (TCGA Network, *Nature*, in press).

HPV-Positive HNSCC

It has well accepted that the clinical features of patients with HPV-driven HNSCC are distinct from HPV-negative disease. This includes distinct sites of origin of the disease (eg. tonsil and base of tongue), younger age and improved relapse-free survival following initial definitive treatment. Clinically, an emphasis on protocol development for patients with

HPV-driven HNSCCs has consisted largely of de-escalation of standard therapy with a lower dose of radiation, more limited resection or de-intensification of chemotherapy.

Initial next-generation sequencing studies of HPV-positive patients confirmed that these individuals harbor few genomic alterations in *TP53* and/or *CDKN2A*, presumably due to the activity of the HPV E6 and E7 viral oncoproteins(11). These studies also suggested that HPV-driven HNSCCs display less genomic complexity as compared to HPV-negative disease, though the TCGA and other more recent cohorts did not confirm this finding, perhaps due to tobacco use in the HPV-positive individuals in these studies. This possibility is supported by the prevalence of both the virally associated Tp*Cp(A/C/T) substitution mutation in the HPV-positive individuals as well as CpG transversions, a mutation class typically associated with smoking. A major limitation in most studies reported to date has been the relatively small numbers of characterized HPV-positive tumors.

HPV-driven HNSCCs are distinct from HPV-negative disease in that they lack focal RTK amplifications but do display a higher rate of focal *PIK3CA* amplification and mutation. *PIK3CA* alterations have been reported as therapeutic biomarkers in this patient population based on cell line and patient-derived xenograft studies(14). HPV-associated HNSCCs also demonstrate enrichment for copy number gains in *TRAF3* and *E2F1* and a lack of *CCND1* amplification when compared with HPV-negative disease.

HPV-driven cancers display both mutations and fusions in the *FGFR3* gene with mutations at position 249 reported at 14% in one study of 50 cases of locoregionally advanced disease and *FGFR3-TACC3* fusions have been reported in multiple cases by TCGA and other groups(15, 23). These two *FGFR3* alterations have been associated with therapeutic response to FGFR small molecule inhibitors in pre-clinical (24) and clinical studies (25, 26) TCGA did not detect any genes displaying statistical enrichment for mutation in HPV-positive individuals as compared to HPV-negative though *B2M* truncating mutations most closely approached significance. In addition to *FGFR3* mutation, other studies have identified the RNA helicase *DDX3X*, which is mutated in medulloblastoma and is a regulator of beta-catenin, as a gene more commonly altered in HPV-positive individuals(15). HPV-positive disease shares many common altered genes and pathways with HPV-negative HNSCC (eg. *NOTCH*, *MLLs*, *RAS*, *WNT*)(15).

In addition to the genomic context in which HPV resides it has become increasingly clear that the virus itself plays an important role in oncogenesis beyond expression of E6 and E7(27, 28). Studies of the interaction of HPV with the human genome in HNSCCs have shown that HPV may be present in integrated or non-integrated forms, may be associated with the presence of absence of ongoing E6/E7 expression and also may be present in extrachromosomal elements. Sites of HPV integration are non-random, occurring in gene- and micro-RNA-rich areas of the genome as well as in sites, which are commonly associated with somatic copy number alterations. HPV integration can have a profound impact on local gene structure and function and result in high-level amplifications, gene disruptions, alternative splicing, novel gene fusions and changes in global promoter methylation and transcription. An intriguing finding in the field of HPV integration is recurrent disruptive integration in the *RAD51* gene, perhaps facilitating further HPV integration by hindering

DNA repair(29). While the study of host genome-HPV interactions is still maturing it is clear that the role of HPV extends beyond the production of E6 and E7 in HNSCCs.

A very important feature of the TCGA data and other cohorts is the demonstration that HPV may be detected in HNSCCs using a number of methods including mass spectrometry and massively parallel RNA and DNA sequencing and that these methods are far more sensitive than those currently applied in the clinic. These methods identify patients without conventional clinical features (e.g. larynx cancers, p16 negative) who appear to have HPV-driven disease. As next-generation sequencing methods are increasingly applied in the clinic it will be a challenge moving forward to further define the sensitivity and specificity of these newer methods for HPV detection and if there is any significance related to quantitative differences in the amount of HPV detected in a given tumor. While p16 immunnohistochemistry is a simple assay, these recent studies suggest that it should not be regarded as an appropriate surrogate for direct assessment of HPV status. p16 assessment alone will misclassify individuals in whom HPV is present in the absence of E6/E7 expression, and more importantly, will overlook HPV in tumors in which both HPV in present and in which p16 is lost by an independent mechanism, an especially relevant issue in patients with both HPV and a tobacco history. For studies moving forward it will be critical to accurately determine HPV status by direct measurement of HPV to avoid systematic errors in patient classification and stratification.

Genomics to Targeted Therapeutics

The application of targeted therapeutics in HNSCCs has been disappointing to date as compared to other cancer types. This has been due in part to the slower development of therapeutic biomarkers and a lack of understanding of the genome landscape of these diseases. As noted above, cetuximab is the only targeted agent approved for HNSCC and its use in the metastatic setting is associated with a low response rate of 10–15% and most studies have failed to find an association between EGFR expression and/or gene amplification with response to EGFR inhibitors including cetuximab in HNSCC cohorts. There are no prospectively validated biomarkers to enable the selection of patients for EGFR-directed therapy.

Prior to the TCGA and other recent studies, earlier reports noted the prevalence of a number of genomic alterations in HNSCCs, which are associated with therapeutic response to targeted agents in other cancers types. These include *EGFR* mutations and *ALK* and *ROS1* fusions. It is now clear that these events are extremely rare in HNSCC, if present at all, and that the therapeutic opportunities in HNSCCs more closely resemble squamous cell cancers from other tissue types. A few specific examples are discussed below.

Fibroblast Growth Factor Receptors

FGFRs have been shown to be activated by amplification, mutation and translocation in a wide range of cancer types. In HNSCC *FGFR1* amplifications are found in HPV-negative patients at a rate of approximately 10% and appear to be enriched in non-oropharynx tumors. *FGFR1* amplification has been associated with therapeutic response to FGFR TKIs in lung squamous cell cancers, though response rates represent only a modest improvement

as compared to chemotherapy(30–32). Multiple explanations for this disappointing result have been reported including the presence of co-mutations activating the *RAS/MAPK* pathway, a lack of correlation with *FGFR1* amplification and expression or activation of the protein and difficulty in standardizing assays for detection of amplification by FISH or NGS methods. Several early-phase clinical trials are ongoing or planned in HNSCC patients with *FGFR1* amplifications who have relapsed/refractory HNSCC (eg. NCT01962532, NCT01004224, NCT01948297) though no public data have been reported on efficacy. Given that FGFR inhibitors appear to be well-tolerated and may also be radiosensitizers, the combination of these agents in the curative treatment setting with the current standard of care may be reasonable in high-risk HPV-negative patients.

FGFR2 and *FGFR3* mutations and *FGFR3-TACC3* fusions are of particular interest as these genetic lesions have been associated with dramatic responses to FGFR TKIs in pre-clinical models and in early phase clinical settings including a case report of a dramatic response to pazopanib in a patient with a *FGFR2* mutated tongue cancer(24). In contrast to *FGFR1* amplification, *FGFR2/3* mutations and *FGFR3* fusions appear to occur largely in HPV-positive individuals at a prevalence of 10–20% and clinical trials are currently targeting this patient population. However, given that these trials are focusing on patients with relapsed/refractory disease they may encounter difficulty with accrual as the number of HPV-positive patients who are candidates for such studies is small.

PI3K/AKT Pathway

PIK3CA is commonly amplified and/or mutated in patients with HNSCCs (37% of cases in TCGA), and *PIK3CA* alterations are enriched in HPV-positive patients. If one examines the PI3K/AKT/mTOR pathway in detail more than one-half of patients with HNSCC have a somatic alteration, which can activate this pathway. As such, there is tremendous interest in developing small molecule inhibitors of components of this pathway for individuals with HNSCC and ample pre-clinical data suggest that this may be an effective therapeutic strategy, though it should be noted that the activity of PI3K inhibitors as monotherapy in lung squamous cell cancers in patients with *PIK3CA* or *PTEN* mutations has been disappointing. However, initial data have been more encouraging when combining these agents with chemotherapy or other targeted agents.

Clinical concepts moving forward include both recruiting patients with relapsed/refractory disease with PI3K pathway lesions as well as using these agents in “window of opportunity” trials in the up-front setting or in combination with chemoradiotherapy (eg, NCT01816984, NCT01195922, NCT01852292, NCT01133678). Pre-clinical data have shown that inhibition of the PI3K pathway may sensitize cancer cells to radiation and that PI3K inhibitors may be most efficacious as radiosensitizers in patients with *NFE2L2* or *KEAP1* mutations, genomic events commonly seen in high-risk HPV-negative individuals(33). A clinical trial in this high-risk population is now ongoing based on these pre-clinical data (NCT02113878).

Cyclin Dependent Kinases

In the TCGA study 32% of HNSCCs displayed an amplification or mutation of *CCDN1*, *CDK4* or *CDK6* with the majority of these alternations found in HPV-negative patients. It should be noted that the genomic region on chromosome 11 containing the *CCND1* locus also contains other cancer-related genes such as *FADD* and it is not clear that *CCND1* is the focus of amplification in all cases with chromosome 11q13 amplification. However, impressive early clinical data in breast cancer have suggested that CDK4/6 inhibitors may be effective in patient cohorts with high rates of *CCND1* amplification and that these agents are well-tolerated as both single agents and in combination with other therapies. Clinical trials are moving forward at this time in other cancer types with frequent alterations of *CCND1/CDK4/CDK6* and a subset of these trials will include patients with relapsed/refractory HNSCC (NCT02101034). Many HPV-negative patients with *CCND1/CDK4/CDK6* amplifications also harbor RTK amplifications, suggesting that combination strategies may be needed in this setting.

Immunotherapy

Immunotherapy approaches have garnered a great deal of excitement in the oncology community based on the early clinical success of immune checkpoint inhibitors in melanoma, renal cell carcinoma and lung cancer. Trials of immunotherapeutic agents are ongoing in HNSCC in both the initial treatment setting with ipilimumab and for recurrent disease with agents targeting the PD1:PDL1 checkpoint and other immune effectors (eg. NCT01860430, NCT01935921) with promising data presented recently with pembrolizumab in relapsed/refractory disease(34). *PDL1* expression is a biomarker reported by some groups to enrich for response to blockade of the PD1:PDL1 checkpoint, and it has been reported in other cancer types, including lymphoma and gastric cancer, that *PDL1* expression is associated with virally-induced cancers(35). While there are several reports on this topic in HNSCCs with variable results, RNA sequencing data from TCGA are consistent with higher levels of *PDL1* expression in HPV-negative individuals. However, it should be noted that these samples contain both tumor and stroma and it is still unclear what the optimal methods are for *PDL1* measurement in the context of patient stratification. In addition to variable expression of *PDL1*, HNSCCs display a wide range of somatic alterations in genes involved in antigen presentation, inflammation and immune evasion including *HLA-A*, *B2M*, *TGFBR2* and *TRAF3*. While the mechanisms governing immune evasion in HNSCCs remain poorly understood it is likely that somatic alterations in these and other genes are likely to play a key role in immune surveillance of HNSCCs and may impact the responsiveness of cancers to specific immunotherapeutic approaches. One particular pathway of interest in this regard is PI3K given reports in other cancer types that it may be associated with response to PD1:PDL1 checkpoint inhibitor therapy(36).

Other targets and strategies

A number of additional therapeutic targets have been proposed for HNSCC based on genomic discovery studies and pre-clinical models. HNSCCs frequently display hyperactivation of STAT3 via a variety of mechanisms and STAT3 pathway inhibitors are currently being explored in both pre-clinical models and in early phase clinical trials.

HNSCCs display frequent degregulation of pro- and anti-apoptotic genes such as *CASP8* and cell line studies have suggested that inhibitors of BCL2 family proteins may demonstrate activity against HNSCCs. HNSCCs also commonly display concurrent amplification of two or more putative “drivers” and pre-clinical studies have demonstrated synergy in combining inhibitors in cell lines with demonstrate multiple activated kinase pathways such as concurrent EGFR and FGFR pathway activation. Novel EGFR-targeting strategies with more potent anti-EGFR TKIs and antibodies are moving forward in HNSCCs as are efforts to better define the subset of patients most likely to benefit from anti-EGFR therapy.

Conclusions and Recommendations

HNSCCs are less common than other cancer types in which substantial strides in biomarker-based clinical trials have been made and the number of clinical trials currently available for individuals with HNSCCs is approximately one-half the number of trials for patients with lung or breast cancers. Further, there are no genetic tests routinely incorporated into the management of HNSCC and patient stratification is largely done based on clinical features and HPV status. With the widespread incorporation of next-generation sequencing diagnostics into the routine care of patients with a wide array of cancer types it will be important to consider how this information can be used to improve the efficacy of therapies for HNSCCs and here we propose a few possible approaches.

First, the molecular alterations identified in the HNSCC TCGA project and other cohorts are not unique and are shared with a number of other epithelial cancer types, most notably lung squamous cell carcinoma. We suggest that clinical trials of novel agents in lung SCCs also include patients with HNSCCs given this overlap and that “basket trial” approaches be considered across these disease types. Natural candidates for this approach include agents targeting FGFRs, PIK3K/AKT, CDKs and immunotherapies. Second, HNSCC would seem to be an ideal cancer type for “window of opportunity” trials, given the relative accessibility of tumor to sample and the widespread use of surgical resection as a standard curative approach. In this study approach, a novel agent could be deployed prior to definitive therapy to assess its efficacy with biopsy samples taken before and during treatment to identify biomarkers of response and resistance. Third, given that we have now defined a number of potential targets in HNSCC the use of these agents in the definitive setting with analysis of tissue before and after therapy should be conducted so that we might better define cohorts of patients for specific therapy approaches in which novel agents may be used in combination with chemoradiotherapy in the initial or adjuvant setting. Finally, it will be critical for the HNSCC community of Surgeons, Radiation Oncologists and Medical Oncologists to appreciate the value of a molecular understanding of HNSCCs to facilitate moving the field forward in the era of genomic medicine.

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Significance

There has been limited success in the use of targeted therapies of patients with head and neck squamous cell carcinomas. Large scale genomic studies have now been conducted which have defined the genomic alterations which drive these cancers. The studies have demonstrated the unique genomic features and diversity of head and neck squamous cell carcinomas and have suggested some initial potential therapeutic targets.

Table 1

Comparison of the common genomic pathway alterations and of specific genomic alterations by functional category in HPV-negative versus HPV-positive HNSCCs.

Genetic Pathways and Alterations	**HPV−**	**HPV+**
RTK Amplification	>20% with ERBB family, FGFR, INS1R	Rare
RTK mutations/fusions	Rare	FGFR2/3 mutations in >10%, FGFR3-TACC3 fusions
H/K/NRAS, NF1	5–10%, HRAS may be most common	5–10%, NF1 loss may be more common
PIK3CA amplification/mutation	Common ~30%	Very common >50%
TP53	Genomic loss in nearly all cases	HPV-driven loss
Cell cycle deregulation	Loss of CDKN2A/RB1 by multiple mechanisms in nearly all cases, CCND1/CDK4/CDK6 amplification common (30%)	HPV-driven CDKN2A loss, E2F1 amplification (20%)
Oxidative Stress Regulation	Common activation of NRF2/KEAP1/CUL3 (25%)	Rare
Differentiation	Common loss of NOTCH1/FAT1/AJUBA, TP63 gain	NOTCH1 loss less common, TP63 gain more common
Immune evasion	Uncommon HLA mutations, <10%	HLA, B2M mutations and TRAF3 loss