HHS Public Access

Author manuscript

Surg Oncol Clin N Am. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Surg Oncol Clin N Am. 2015 July ; 24(3): 397–407. doi:10.1016/j.soc.2015.03.002.

Molecular Biology and Immunology of Head & Neck Cancer

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Synopsis

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. In addition, the discovery of human papillomavirus (HPV) in relationship with oropharyngeal squamous cell carcinoma has shifted our molecular understanding of the disease. New investigation into the role of immune evasion in HNSCC has also led to potential novel therapies based on immune specific systemic therapies.

Keywords

Molecular biology; Targeted therapy; Immunology; Head and Neck Cancer

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 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 HNSCC

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

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Recently, human papillomavirus (HPV) has been associated with a subset of HNSCC, chiefly in the oropharynx and primarily in younger, white, non-smokers.[3,6] HPV is a double-stranded DNA virus which infects the squamous epithelium. High-risk subtypes, particularly HPV-16 and HPV-18, are associated with development of malignancy, 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 of cohort of sequenced tumors studied.[10]

Gene mutations were segregated by HPV tumor status. HPV-positive tumors harbored fewer mutations compared to HPV-negative tumors. [1,10,11] TP53 mutations were found almost exclusively in HPV-negative tumors [1,10] while activating mutations and amplifications of PIK3CA were commonly seen in HPV-positive tumors (figure 1).[10] This is consistent with prior data showing the same distinct genetic alterations.[12]

Beyond sequencing, gene promoter methylation of several genes including CDKN2A, CDH1, MGMT, DAPK1 has been established in oral squamous cell carcinoma.[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 gene encodes for the p53 protein, “guardian of the genome.” TP53 is one of the most frequently mutated genes in HNSCC[1,2,10,15] 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, which inactivates and degrades p53.[18] The CDKN2A locus at 9p21 codes for two alternatively spliced proteins p14ARF and p16INK4A, which both regulate p53 function.[19] (Figure 2)

A majority (50–63%) of p53 mutations in HNSCC 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 wildtype 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, CDKN2A was found to be mutated in 9–12% of tumors.[1,2] Loss of heterozygosity is frequently seen at the CDKN2A locus in HNSCC, including premalignant lesions.[25] The p16 protein is also significant (overexpression is consistently seen in HPV-related oropharyngeal cancers).[26] The mechanism is related to the inactivation of Rb by the E7 viral protein, resulting in unregulated overexpression of p16.[27]

EGFR, Ras and PI3K

Epidermal growth factor receptor (EGFR) is part of the ErbB family of receptor tyrosine kinases. After ligand binding (EGF or TGF-α), activated EGFR forms a dimer and activtes downstream pathways. These include PI3K/Akt and Ras pathways that promote cell growth, proliferation and inhibit apoptosis (Figure 3). Activation of PI3K results in conversion of phosphatidylinositol biphosphate (PIP2) to phosphatidylinositol triphosphate (PIP3). PIP3 can then bind and phosphorylate Akt, triggering inhibition of apoptosis, mTOR activation and activation of MDM2.[28] PTEN negatively regulates this signaling by dephosphorylating PIP3 to PIP2. thus preventing downstream signaling.

In HNSCC, overexpression of the EGFR gene is seen in about 90% of tumors.[29] Increased EGFR expression correlates with increased local recurrence[30] and worse overall survival.[30,31] EGFR overexpression plays a clear role in HNSCC; interestingly, few mutations have been observed in EGFR[11,29] (Figure 1). HRAS, a target downstream of EGFR, is mutated in 4–5% of tumors.[1,2,10]

In HNSCC, PI3KCA (catalytic subunit of PI3 kinase) is mutated in 6–21% of tumors.[1,2,32] Advanced stage HNSCC harbor increased mutations along the PI3K pathway.[33] PI3K pathway genes are the main genes mutated in HPV-related tumors[10,33] (Figure 1).

NOTCH Signaling

Notch is a cell surface receptor that binds to ligands on an adjacent cell surface, such as Jagged or Delta.[28] Next, proteolytic cleavage releases an intracellular fragment that travels to the nucleus. affecting gene transcription. Downsteam targets include HES1 and HEY1, which promote cell cycle progression and survival.[34]

Inactivating mutations of NOTCH1 were found in 10–19% of head and neck tumors.[1,2,10] This suggests that NOTCH1 acts as a tumor suppressor in HNSCC. In oral squamous cell carcinoma (SCC) cell lines, reactivation of the wild type NOTCH1 gene blocked cell proliferation.[35] However, NOTCH1 also acts as an oncogene in hematologic malignancies.[36] Within sequencing data of HNSCC, some mutations in NOTCH1 were not inactivating, suggesting that its role in HNSCC may be mixed.[32,37] Recent data have shown that a subset of HNSCC tumors actually show downstream activation of NOTCH.[37]

Apoptotic pathways

Apoptotic pathways are regulated by intrinsic signals (such as p53) or extrinsic signals through cell surface receptors. Multiple signals such as p53 response to DNA damage, UV radiation, or influx of calcium ions can trigger apoptotic signaling. When the balance tips towards apoptosis, cytochrome c is released from the mitochondria, and the caspase cascade

executes programmed cell death. Cell surface receptors, such as FAS and death receptors, may also trigger apoptosis through activation of caspase 8 and downstream caspases.[28]

With head and neck cancer, mutations in caspase 8 (CASP8) have been observed in 8–9% of tumors[2] (TCGA data) with a majority occurring in oral cavity SCC.[10] TRAF3, BIRC2 and FADD interact with the cell surface death receptors and were found to harbor mutations in head and neck cancer.[10] TRAF3 mutations were noted primarily in HPV-positive tumors.

Implications for targeted therapy

Current chemotherapy treatments for head and neck cancer are not targeted, but instead platinum based treatments (primarily cisplatin and carboplatin) with concurrent radiation are the mainstay of treatment.[38]

Therapies targeting EGFR

The main targeted therapy currently available for HNSCC is Cetuximab, an anti-EGFR IgG1 antibody. Cetuximab was approved for the treatment of HNSCC after a study showed significantly improved progression-free and overall survival when concurrent Cetuximab with radiation was compared to radiation alone.[39] Recent data have not shown improved outcomes when combining cetuximab with concurrent cisplatin in primary chemoradiation.[40] Questions still remain regarding the mechanism of Cetuximab activity. Despite frequent EGFR overexpression, response rates to cetuximab as a single agent are around 10–15% in recurrent HNSCC[41] and efficacy has not been found to correlate with EGFR expression.[40,42]

Other anti-EGFR antibodies (Panitumumab, Zalutumumab, Nimotuzumab) have shown promising results in preclinical studies.[43] In phase II clinical trials, Panitumumab did not show improvement in overall survival,[44] and the efficacy of the other antibodies has yet to be determined (Clinical trials: NCT01054625, NCT00401401, NCT01425736).

FDA approved small molecule tyrosine kinase inhibitors (TKI) of EGFR in other cancers include gefitinib, Erlotinib, Lapatinib, and Afatinib.[43] In preclinical studies, these TKI treatments have been shown to increase cell death in response to radiation therapy, especially when combined with VEGF inhibitors.[45,46] In clinical trials, they have not been shown to improve outcomes,[47,48] but lapatinib may improve progression free survival in HPV-negative patients.[49]

VEGF and other tyrosine kinase inhibitors

Inhibition of VEGF may sensitize HNSCC to radiation treatment.[50] However, treatment with Bevacizumab, an anti-VEGF antibody, has not shown improved outcomes. Importantly in clinical trials, it was associated with locoregional progression[51] as well as increased incidence of osteoradionecrosis.[52]

Small molecule TKIs with multiple kinase targets approved for other cancers include vandetanib, sunitinib, sorafenib and dasatinib.[43] Preclinical studies of these TKIs in HNSCC

have shown promise, particularly in increasing radiation-induced cytotoxicity.[53–55] Ongoing trials have not yet shown significant clinical results.[56,57]

PI3K and mTOR inhibitors

The PI3K/mTOR pathway is another potential target in HNSCC, highlighted in recent genomic data (Figure 1, TCGA). Preclinical studies of BEZ235, a small molecule inhibitor of PI3K and mTOR, have shown efficacy in head and neck cells harboring PIK3CA mutations[33] and it may be more effective for HPV related tumors.[58] Rapamycin and Everolimus, mTOR inhibitors that have been used for transplant immunosuppression, are currently under clinical trial investigation in HNSCC patients (NCT00935961, NCT01283334, NCT01195922).

Immunology

Recent studies have explored the role of immune system evasion in the progression of HNSCC.[59] One major pathway of interest is the co-signaling of the programmed cell death protein 1 (PD-1) and its ligand (PD-L1). PD-L1 is normally expressed by antigen presenting cells and is overexpressed in solid tumor cells.[60] The interaction between PD-1 and PD-L1 dampens the immune response.[60] Currently, antibodies directed towards PD-1 and PD-L1 are in clinical trials for patients with other solid tumors. Recently Nivolumab, a IgG4 monoclonal anti-PD-1, has shown dramatic results in advanced melanoma and is undergoing review with the FDA.[61] HNSCC tumors, especially HPV-positive tumors, show increased expression of PD-L1.[62] However, PD-L1 expression in head and neck tumors has not been clearly associated with clinical prognosis.[59] Clinical trials are beginning to investigate Pembrolizumab (anti PD-1) in head and neck cancer (NCT02255097, NCT02252042).

Another potential method of immune system modulation currently under investigation is with use of phosphodiesterase-5 (PDE5) inhibitors, such as tadalifil. PDE5 inhibitors act by increasing cGMP to inhibit myeloid derived suppressor cells (MDSC), which may dampen immune response to tumors.[63] Preclinical studies showed that treatment with tadalifil reduced tumor growth.[63] In head and neck patients, tadalifil has been shown to significantly decrease T-regulatory and MDSC in patient serum[64] and phase II trials are currently accruing to ascess treatment efficacy (NCT01697800).

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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 distinct genetic profile
- Genetic sequencing of head and neck cancer revealed mutations in key cancer pathways including p53, EGFR/Ras/PI3K, NOTCH, and apoptotic pathways
- Therapies targeted towards these pathways are limited but under investigation
- Head and neck cancers may progress by immune evasion, which is another targetable mechanism

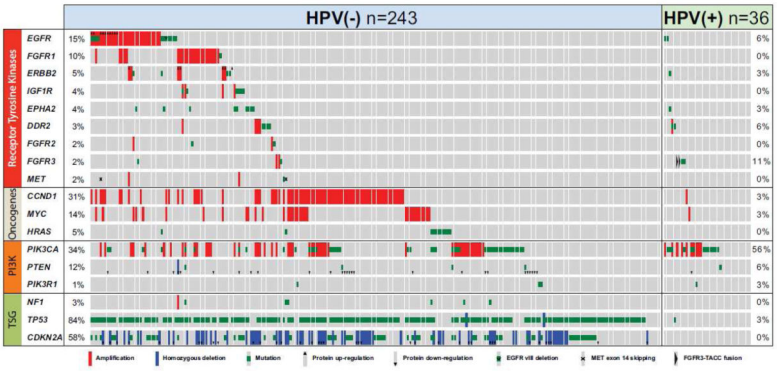

Figure 1.

Genetic alterations in key oncogenic pathways from TCGA. (From Hayes, N et al. The Cancer Genome Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature, in press. 2014, with permission.)

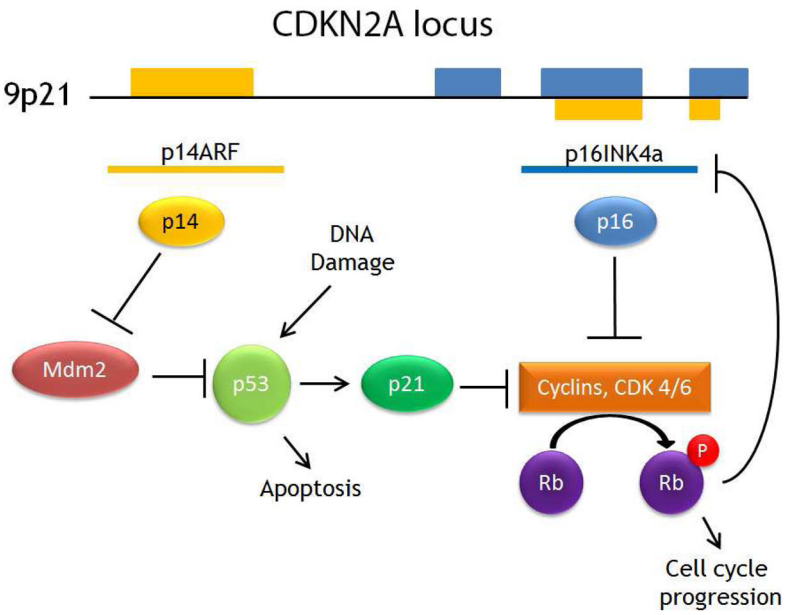

Figure 2. CDKN2A gene products and p53 regulation

CDKN2A codes for alternatively spliced p14ARF and p16INK4a genes. The p14 protein inhibits MDM2, which ubiquitinates p53. Both p21, induced by p53, and p16 inhibit cyclins that promote cell cycle progression through phosphorylation of retinoblastoma protein (Rb). Rb feeds back to inhibit p16 production.

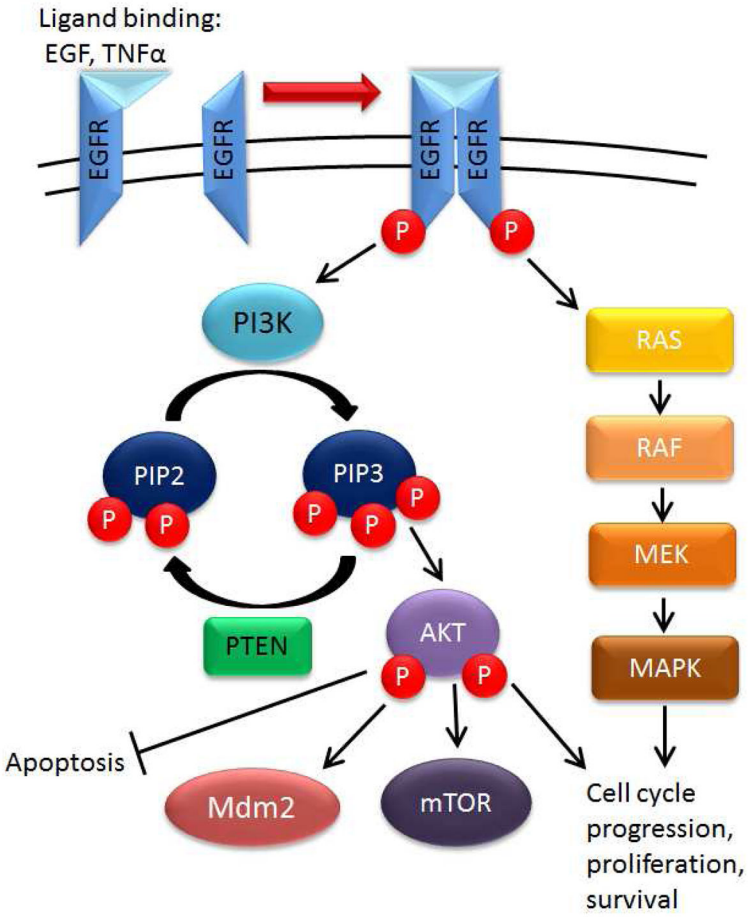

Figure 3. EGFR signaling and downstream pathways

When an extracellular ligand binds to EGFR, dimerization occurs, promoting cross phosphorylation. This activates Ras signaling and activates PI3K to produce PIP3. PIP3 phosphorylates Akt which promotes mTOR signaling, promotes MDM2 (inhibits p53) and inhibits apoptosis.

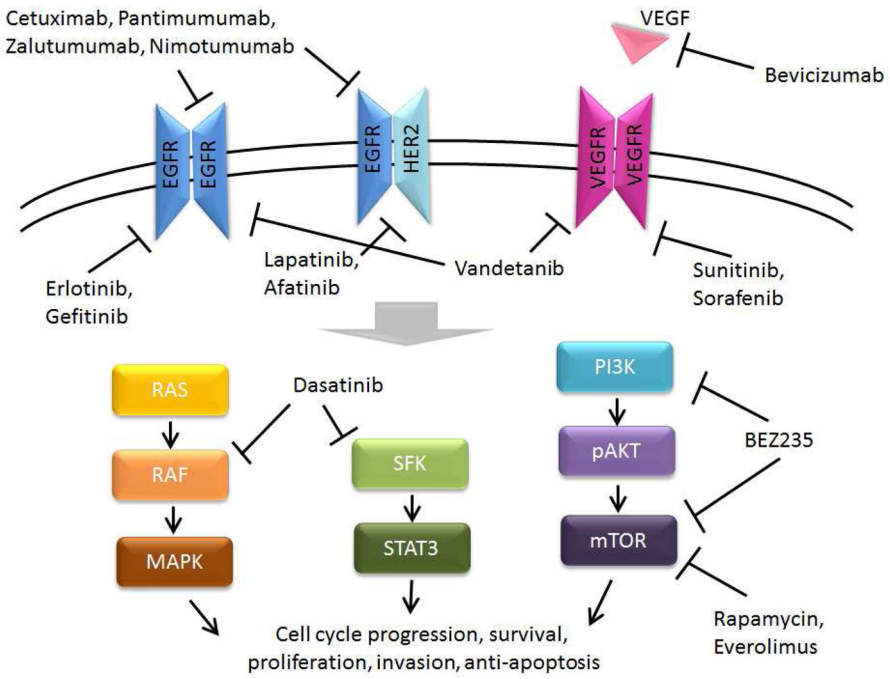

Figure 4. Potential targets for therapy in head and neck cancer

SFK= Src family kinases.

(Adapted from Du Y, Peyser ND, Grandis JR. Integration of molecular targeted therapy with radiation in head and neck cancer. Pharmacology & therapeutics. Apr 2014;142(1):88–98, with permission.)