Review

Clinical Cancer Research

Head and Neck Carcinoma Immunotherapy: Facts and Hopes

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Abstract

Cancer of the head and neck (HNC) is a heterogeneous disease of the upper aerodigestive tract, encompassing distinct histologic types, different anatomic sites, and human papillomavirus (HPV)–positive as well as HPV-negative cancers. Advanced/recurrent HNCs have poor prognosis with low survival rates. Tumor-mediated inhibition of antitumor immune responses and a high mutational burden are common features of HNCs. Both are responsible for the successful escape of these tumors from the host immune system. HNCs evolve numerous mechanisms of evasion from immune destruction. These mechanisms are linked to genetic aberrations, so that HNCs with a high mutational load are also highly immunosuppressive. The tumor microenvironment of these cancers is populated by immune cells that are dysfunctional, inhibitory cytokines, and exosomes carrying suppressive ligands. Dysfunctional immune cells in patients with recurrent/metastatic HNC can be made effective by the delivery of immunotherapies in combination with conventional treatments. With many promising immune-based strategies available, the future of immune therapies in HNC is encouraging, especially as methods for genetic profiling and mapping the immune landscape of the tumor are being integrated into a personalized approach. Efficiency of immune therapies is expected to rapidly improve with the possibility for patients' selection based on personal immunogenomic profiles. Noninvasive biomarkers of response to therapy will be emerging as a better understanding of the various molecular signals co-opted by the tumors is gained. The emerging role of immunotherapy as a potentially beneficial addition to standard treatments for recurrent/metastatic HNC offers hope to the patients for whom no other therapeutic options exist. *Clin Cancer Res; 24(1); 6–13. ©2017 AACR.*

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) accounts for about 3% to 5% of all cancers in the United States, with an estimated frequency of 61,760 new cases in 2016 and 13,190 deaths (1). More than 600,000 cases of HNSCC are diagnosed annually worldwide (2). Primary risk factors for HNSCC include tobacco, alcohol, and human papillomavirus (HPV) infection. Despite considerable progress made in the use of chemotherapy, radiation, and targeted therapies, the treatment of advanced or recurrent head and neck cancers (HNC) remains largely ineffective. The 5-year survival rate of patients with HNC has not improved for many years and remains at 50% for patients with locoregionally advanced disease (3). The development of drug resistance continues to be a major therapeutic hurdle. Recurrent/metastatic HNCs that do not respond to platinum-based chemotherapy progress very rapidly and have very poor prognosis with no other therapeutic options available. The development of new therapeutic strategies for HNC is an unmet need with the highest priority. Immune-based therapies appear to offer a new, potentially effective strategy that could alter the therapeutic landscape of HNC. By preventing tumor immune escape and stimulating antitumor immune responses to keep the residual tumor cells in check, immune therapies are effective in prolonging patients' survival. Also, tumors that become resistant to chemo- or radiotherapy often remain sensitive to immune-mediated mechanisms.

The hypothesis underpinning the use of immunotherapies for HNC patients with advanced or recurrent disease assumes that ineffective antitumor immune responses can be made effective by an initial tumor ablation followed by delivery of immunologic agents that selectively block inhibitory mechanisms and stimulate antitumor immune responses. There are currently numerous therapeutic strategies available for testing this hypothesis, and some are being tested in clinical trials for patients with HNC.

The Tumor Microenvironment in HNC

HNC, like all other cancers, results from a stepwise accumulation of genomic instability, chromosomal aberrations, and genetic mutations (4). Within cancer tissues, arising mutant cells strive for resources and space; avoid immune surveillance; and, in collaboration with the extracellular matrix (ECM) elements, establish their own unique niche. The niche, in addition to neoplastic cells, incorporates the tumor stroma (fibroblasts, endothelial cells, pericytes, and mesenchymal cells), immune cells [T cells, natural killer (NK) cells, B lymphocytes, macrophages, polymorphonuclear leukocytes (PMN), and mast cells], blood vessels, and a host of immunoinhibitory-soluble or membrane-bound factors (5). The cells within the tumor microenvironment (TME) are reprogrammed by the tumor to aid its progression or to shield cancer cells from the host immunity. Seen in this context, the TME is a dynamic complex of cells and soluble factors contributing to tumor drug resistance, interfering with oncologic therapies and promoting tumor cell growth. *In situ* studies of

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human tumors suggest that each tumor creates its own TME that distinguishes it from other tumors with the same histopathology. Most HNCs share the squamous cell origin; yet because they arise in various tissue locations such as the throat, larynx, nose, sinuses, the oral cavity, or the oropharynx, these cancers are highly heterogeneous, and the TME of each individual tumor is unique. Furthermore, HNCs are either HPV^+ or HPV^-, and the viral origin further introduces differences that are reflected in different susceptibility of these tumors to therapy and in patient survival (6). The HPV^+ cancers have better outcome than HPV^- HNCs, and it has been speculated that this reflects better activity of the immune system conditioned by the virus. High levels of regulatory T cells (Treg) and $PD1^+$ T cells in HPV^+ patients were shown to correlate with favorable outcome (7, 8), suggesting that strong reactivation of immune response to the virus is being tempered by the host immune system. Interestingly, the benefit of HPV infection extends only to HPV^+ oropharyngeal cancers and not to other infection sites (9), an indication that local immune response to the virus and the TME shape cancer outcome. The TME is never static and always changes to deal either with host defense or with therapeutic interventions. Similar to HPV-1 infection, therapies are known to alter the content of the TME (10). Thus, a primary HNC examined prior to any therapy has different phenotypic and functional profile from that of the same tumor examined after chemotherapy, radiotherapy, or targeted therapy. It follows that changes induced by conventional therapies in the cellular and molecular content of the TME might be useful as biomarkers to inform selection of antitumor immune therapies.

The Immune Profile of HNC

Immune dysfunction in HNC has been extensively reviewed (5). It encompasses many different phenotypic and functional changes in immune cells that occur with a different frequency in patients with early- versus late-disease stages (11). HNC is one of the most immunosuppressive human tumors. Whereas accumulations of $CD3^+CD4^+$ or $CD3^+CD8^+$ effector T cells in the tumor correlate with better prognosis in some studies (7), others report selective apoptosis of activated tumor antigen (TA)–specific $CD8^+$ T cells, rapid turnover of effector T cells, and functional paralysis of T, B, NK, or dendritic cells (DC), all of which predict poor outcome (11, 12). Accumulations of Tregs or of myeloid-derived suppressor cells (MDSC) or of adenosine-producing regulatory B cells (Breg) at the tumor site or in the peripheral circulation of patients with HNC also associate with poor outcome (13, 14).

Interestingly, in the TME of patients with HNC, $CD25^+FOXP3^+$ Tregs overexpress CTLA-4, PD-1, TIM-3, and TGFβ-associated LAP on the cell surface and upregulate suppressor functions (15). This finding implicates Tregs in downregulation of antitumor immunity. Molecular mechanisms that these Tregs or other regulatory cells utilize for mediating immune suppression in HNC are listed in Table 1. This list includes inhibitory pathways known to be overexpressed in HNC and to contribute to local or systemic immune suppression. Furthermore, activation of these inhibitory pathways exerts strong suppressive effects on various immune cells and their development. Figure 1 illustrates how immunomodulatory ligands or cytokines, which are elevated in HNC, can skew differentiation of T cells, contributing to immune dysfunction. Subversive effects of ADO and prostaglandin E_2 (PGE_2) on immune cell functions in HNSCC are well-documented (16, 17). Recently, the presence of JAG-1, a Notch ligand, in the TME of HNC has been noted and its negative impact on immune cells is under study (18). Also, tumor-derived exosomes, the smallest of extracellular vesicles (30–150 nm) in plasma of patients with HNC, carry most of the aforementioned inhibitory ligands and inhibit immune cell functions. Exosomes, conveyors of suppressive molecules from the tumor to immune cells, may potentially serve as predictors of response to therapy or of outcome and are of special interest in the context of cancer immunotherapy.

Current Clinical Efforts to Diminish Tumor-Induced Immune Suppression in HNC

Given the extent and variety of immune dysfunction mechanisms operating in HNC (Table 1), it is not surprising that efforts to

Table 1. Molecular pathways overexpressed in the microenvironment of HNCs mediate immune suppression

Dysregulated signaling pathways	Effects of signaling on immune or tumor cells	References
EGF/EGFR	↑ Tumor resistance to immune attack	5
	↑ Production of inhibitory factors/cytokines	
	↑ Suppressor functions in Tregs	
IL6, EGF, and VEGF/STAT3	↑ Tumor resistance to immune attack	59–63
	↑ Production of inhibitory factors/cytokines	
	↓ DC maturation	
	↓ Cytolytic activity of CTL and NK cells	
COX-2/PGE_2	↑ Tumor resistance to immune attack	
	↓ Immune cell functions via cAMP-mediated signaling	16, 17
PI3K/COX-2/PGE_2	↓ Survival of immune cells	
PD-1/PD-L1	↑ Autocrine tumor signals and survival	15, 64–67
	↓ Antitumor functions of T cells, B cells, NK cells, and monocytes	
	↑ Treg expansion and suppressor functions	
TGFβ/TGFβRI + RII	↑ Tumor growth	42, 43, 68
	↓ Functions of $CD8^+$Teff polarization of $CD4^+$ T-cell differentiation toward Treg and TH17 cells	
Adenosine/$A_{2A}R$	↓ T-cell functions via cAMP-mediated signaling	44, 69
CD39/CD73 ectoenzymes	↑ Adenosine production	44, 70
	↑ $A_{2A}R$ signaling	
	↓ Functions of immune cells	
Fas/FasL	↑ Apoptosis of activated $CD8^+$Teff cells	12
JAG-1/NOTCH-1	↑ Tumor resistance to immune attack	18, 71
	↓ Functions of immune cells	
	↑ Treg proliferation	

Abbreviations: CTL, cytotoxic T lymphocytes; Teff, effector T cells.

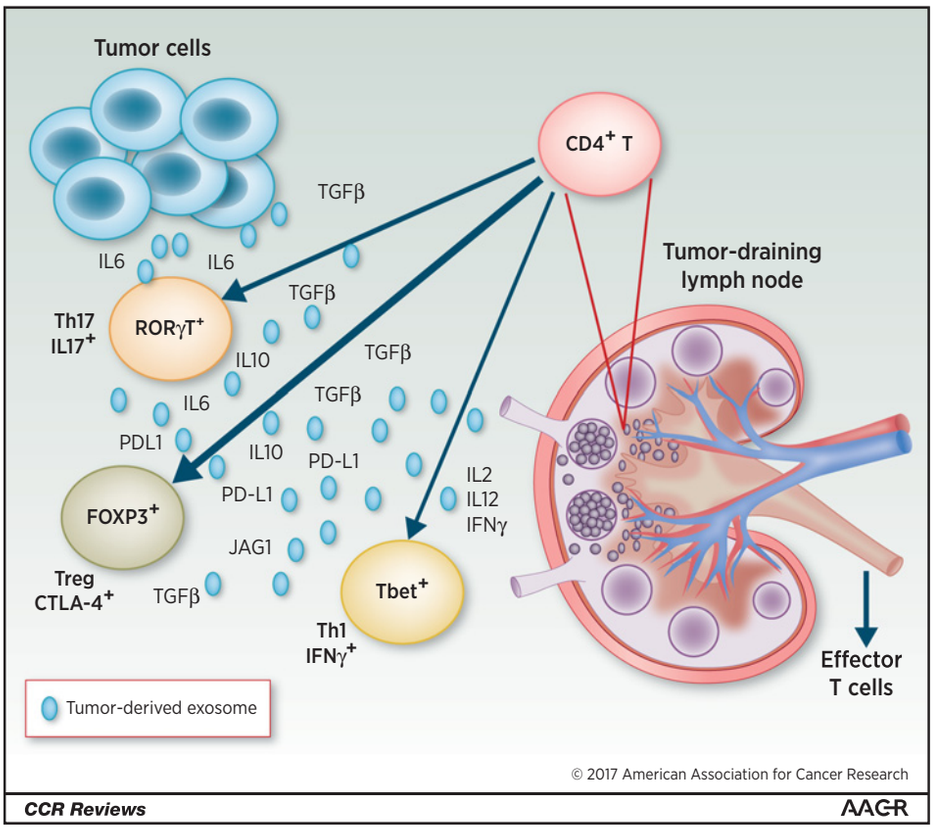

Figure 1.
The TME of HNCs is rich in lymph nodes that drain the tumor but also serve as key immune organs for T-cell differentiation, maturation, and interaction with DC-presenting TAs. The milieu of the tumor-draining lymph nodes is saturated by tumor-derived inhibitory factors (TGFβ, IL10, IL6, PD-L1, and JAG-1) and is deficient in IL2 and IFNγ. In this cytokine milieu, T cells are polarized to differentiate into Treg or Th17 lineages and away from the IFNγ-producing Th1 effector cell phenotype. As a result, tumor-infiltrating lymphocytes are enriched in Tregs and proinflammatory Th17 cells but lacking in Th1 antitumor effector cells. The skewed differentiation of T cells in the TME results in dysregulation of antitumor immunity. Tbet, RORγt, and FOXP3 are transcription factors that determine T-cell lineages. Tumor-derived exosomes carrying immunosuppressive cargoes contribute to the inhibitory environment.

counteract tumor-induced suppression and achieve immune reconstitution have been only moderately successful to date.

Cytokines

Cytokines were the first immunotherapies tested in HNC (19). In 1994, beneficial effects of peritumoral delivery of IL2 in oral HNC were reported (20). Furthermore, in a randomized phase III trial of IL2 given perilymphatically after surgery to patients with the oral cavity cancers, >25% improvement in overall survival (OS) at 5 years was reported (21). In contrast, systemic delivery of IL2 in another trial was ineffective (22). Perilymphatic delivery of IRX-2, a mixture of low-dose IL2, IL1β, IL6, IL8, IFNγ, TNFα, G-CSF, and GM-CSF, was tested in a phase II study for patients with previously untreated, resectable stage II to IV HNSCC (23). Toxicities were tolerable. IRX-2, given preoperatively for 21 days in combination with cyclophosphamide and indomethacin as immune adjuvants, was effective, inducing responses in 16% of patients, with evidence for increases in lymphocytic infiltrates in the responding tumors (24). In the randomized phase II trial, the safety and efficacy of IRX-2 delivered in the neoadjuvant setting was confirmed, and the immune benefits were correlated to improved 5-year survival (25). Systemic administration of other cytokines and IFNs to patients with HNC demonstrated limited efficacy and had significant toxicity (26). It is worth noting that perilymphatic delivery of cytokines with intent to alter the environment of the tumor-draining lymph nodes appeared to be more successful and better tolerated than systemic delivery of cytokines. Among the cytokines tested in HNC, IL6 emerged as a key player in modulating antitumor immune responses, and it may be potentially useful as a prognostic biomarker in HNC (27).

Cancer vaccines

Cancer vaccines are designed to activate TA presentation by antigen-presenting cells (APC) to T cells. Vaccines using TAs that are tumor-specific and essential for tumor cell survival are preferable. As no such nonmutated tumor-specific antigens are available for HNC, whole tumor cell vaccines or vaccines targeting tumor-associated antigens were used, all of which yielded modest results. Vaccination strategies included protein or peptide vaccines, DNA-based vaccines encoding TAs, or recombinant viral or bacterial vector-based vaccines containing TA-encoding DNA (28). The HPV vaccines containing bacterial vectors, for example, vaccinia-based E6/E7 vaccines, showed that patients with HNC were able to generate virus-specific cytotoxic T lymphocytes (CTL), but this did not translate into robust antitumor responses or better outcome (29). Interestingly, a recent report on RNA sequencing (RNA-Seq) and whole-genome sequencing (WGS) in HPV^+ HNCs showed that three fourth of these cancers down-regulate expression of E6 and instead express E2 (30). This would suggest that E1/E2 might be better therapeutic targets than E6/E7 and could explain limited efficacy of current therapeutic vaccines for HPV^+ cancers. In contrast to therapeutic vaccines, prophylactic vaccines for HPV, aimed at eliciting virus-neutralizing antibodies to prevent initial infection, are showing promising results (31). Systemic or intratumorally delivered vaccines containing *ex vivo*–generated autologous DCs pulsed with synthetic peptides (32) or loaded with tumor-derived proteins or tumor cells (33) were tested for toxicity and efficacy in patients with HNC. They were found to be nontoxic, feasible but rather laborious to prepare, and largely not efficacious despite multiple repeated deliveries to patients with advanced HNC (32). In aggregate, experience with

therapeutic HNC vaccines suggests that the immunogens selected for vaccinations and/or adjuvants used to improve vaccine immunogenicity were not effective in the tolerogenic TME of HNC.

Monoclonal antibodies

Monoclonal antibodies (mAb) targeting the tumor, its components, and products or tumor-induced regulatory cells are the most widely used immunotherapy to date in HNC. Cetuximab, a mouse–human chimeric immunoglobulin G1 (IgG1) antibody targeting EGFR was approved by the FDA for therapy of HNC in 2006. EGFR is overexpressed in 80% to 90% of HNSCC and upon binding of EGF promotes tumor cell proliferation, angiogenesis, and metastasis. However, cetuximab therapy is effective in only 10% to 20% of patients with HNC (34). Mechanisms underlying differential clinical responses to cetuximab are unrelated to EGFR expression levels. Cetuximab mediates antibody-dependent cytotoxicity (ADCC), and, in addition to activating NK cells for cytotoxicity, it promotes NK cell–DC cross-talk and upregulates the antigen-processing machinery in DCs and priming of TA-specific $CD8^+$ T cells (35). Cetuximab also increases the frequency and suppressor functions of $CD4^+CD39^+CD25^+$ Tregs but only in patients with HNC who are nonresponders to therapy (36). As Tregs suppress functions of NK cells, which mediate ADCC, and of newly induced TA-specific CTLs, expansion of Tregs by cetuximab might account for patients' unresponsiveness to therapy. Panitumumab, a fully humanized mAb specific for EGFR, was used for therapy of patients with recurrent or metastatic HNC in the phase III SPECTRUM trial comparing cisplatin and fluorouracil with or without panitumumab (37). The results showed improved progression-free survival (PFS), but not OS. This contrasted with the results of EXTREME study, where patients were randomized between cisplatin (or carboplatin) and 5-fluorouracil with or without cetuximab. In this trial, OS was improved in patients receiving chemoimmunotherapy (38). The outcome differences observed between panitumumab and cetuximab, both of which bind to EGFR, illustrates the complexity of the immune interactions in the TME, calling attention to the need for a better understanding of cellular/molecular mechanisms that are invoked by immunotherapies in patients with HNC.

Immune Checkpoint Blockade in HNC

Current immunotherapy of HNC is focused on targeting T-cell–inhibitory receptors that function as immune checkpoints responsible for maintaining the balance between activation and inhibition of immune responses. Tumors have learned to co-opt the immune checkpoints as a major mechanism of resistance. The inhibitory receptors, CTLA-4, PD-1, and others, act as breaks guarding against the danger of excessive, potentially dangerous, T-cell activation. In the TME, numbers of these receptors on T cells increase as does their suppressive function (15). The immune checkpoint inhibitors (ICI) that block CTLA-4 (e.g., ipilimumab) or PD-1 (e.g., nivolimumab and pembrolizumab) release the breaks imposed by tumor-derived signals and allow for T cells to resume their immune activities. In phase III clinical trials (CHECKMATE-141 or KEYNOTE-012), anti–PD-1 antibodies were shown to successfully rejuvenate antitumor immunity and produce durable clinical responses in a subset of HNC patients with refractory/metastatic HNC (39, 40). The overall clinical experience from several trials with different ICIs indicates that only some patients (~15%) with refractory/metastatic HNC achieved durable remissions and prolonged survival (41). Although most patients with advanced HNC do not respond to ICIs, PD-1–targeted therapies are emerging as standard of care for platinum refractory/metastatic HNC. This said, it is important to note that some of the observed clinical responses occurred in patients with HNC whose tumors expressed minimal levels or no PD-L1 (39). Thus, it is unclear why only some patients respond to PD-1/PD-L1–targeted therapy. Given the lack of any therapy for patients with HNC who do not respond to anti–PD-1 antibodies, there is an urgent, unmet need to identify the molecular determinants in the TME that are responsible for resistance to ICIs.

Targeting Other Immunoinhibitory Mechanisms in HNC

Subversion by the tumor of immune checkpoints is but one way of orchestrating immune escape. The therapeutic efficacy of ICIs may be limited because immune dysfunction in the TME of HNC is mediated by other tumor-driven mechanisms (see Table 1). IHC of HNC specimens shows that these tumors produce a wealth of immunoinhibitory factors, including IL10, TGFβ, arginase, PGE_2, and others (5). Among these, TGFβ has been shown to attenuate the activity of $CD8^+$ T cells and skew the differentiation of $CD4^+$ helper T cells (Th1) toward Tregs and Th17 cells (Fig. 2), which promote tumor growth and limit development of central memory T cells (42). About 50% of patients with HNC lose SMAD4 activity via inactivating mutations or loss of heterozygosity (LOH), which leads to elevated TGFβ levels and HNC formation in mice (43). Thus, in the TME of HNC, TGFβ significantly contributes to immune dysfunction and is an important therapeutic target. The ADO pathway is a well-known contributor to immune dysfunction in HNC (44) and is viewed as a significant barrier to effective immunotherapies. Pharmacologic inhibitors, siRNAs, or antibodies specific for the components of this pathway or for ADO receptors show efficacy in preclinical studies and are entering the clinical arena. Several strategies for blocking ADO, including inhibitors of ectonucleotidases, CD39, and CD73, are currently in clinical trials. Data from a recent trial with MEDI9447, a mAb that blocks CD73 and ADO synthesis, showed that the observed inhibition of tumor growth was associated with the reversal of ADO-mediated T-cell suppression (45). In the TME of HNC, ADO may operate in synergy with the COX-2/PGE_2 pathway, which is overexpressed in HNC and has been linked to HNC progression and poor outcome (15). PGE_2, a product of COX-2 activity, binds to four G-protein–coupled receptors on responder cells, and its signaling leads to cAMP-dependent suppression of immune cell functions (15). Attempts to block PGE_2-mediated suppression *in vivo* by using COX-2 inhibitors (e.g., rofecoxib and celecoxib) in HNC induced antitumor effects and restored antitumor immunity but were abandoned due to unacceptable toxicity (46). More recently, the chronic use of nonsteroidal anti-inflammatory drugs (NSAID) was reported to be associated with improved disease-free survival (DFS) and OS in patients with stage III colorectal cancer whose tumors overexpressed COX-2 (47). It has been suggested that chronic intake of aspirin might have similar salutary effects in HNC.

Activation of Immune Cells in HNC

As immune checkpoint inhibitors release T cells from tumor-imposed suppression, survival and antitumor functions of these

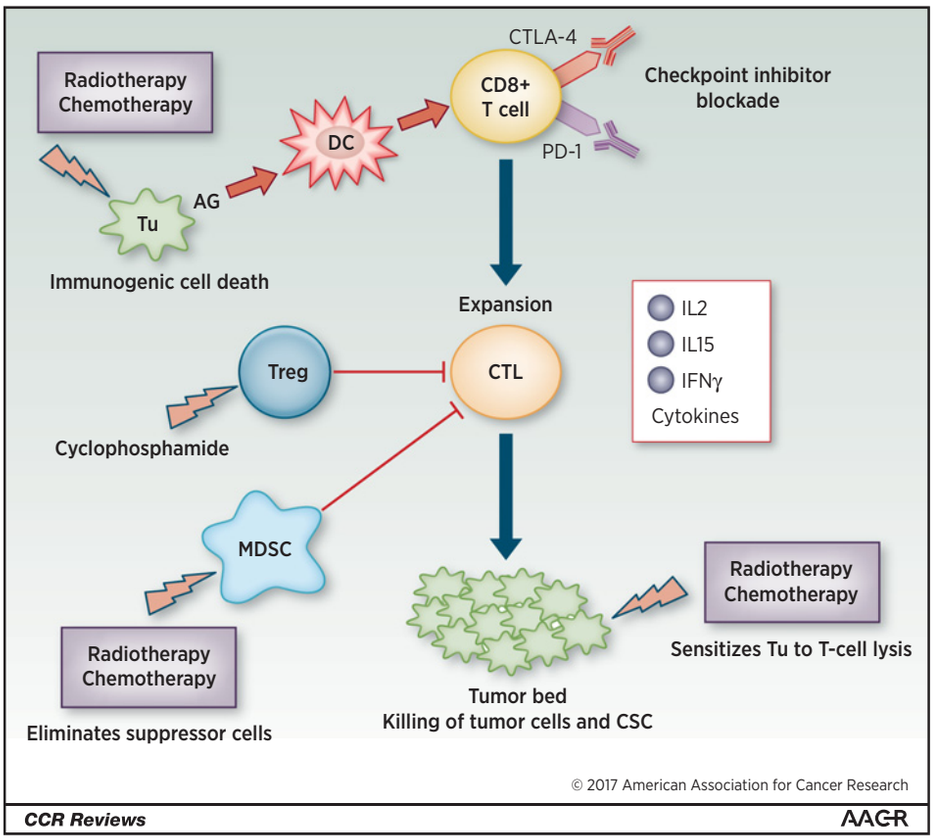

Figure 2.
The rationale for combination of immunotherapy with conventional antitumor therapy. The conventional therapy for HNC can (i) induce immunogenic death of tumor cells and release TAs that can be successfully processed and presented to T cells by DCs, (ii) eliminate or decrease the numbers of Tregs or MDSCs that interfere with antitumor activity of T cells, and (iii) sensitize tumor cells to lysis by immune effector cells. The subsequent blockade of immune checkpoints (CTLA-4 and PD-1) allows tumor-reactive T cells to expand and exercise antitumor activities. This requires further modification of the TME and the delivery of cytokines that are necessary for the expansion of tumor-reactive T cells and for the maintenance of their antitumor functions. Ultimately, these CTLs will be responsible for elimination of residual tumor cells. Conventional therapies not only eliminate tumor cells, providing a pool of antigens for presentation to T cells, but also set the stage for immune cells rejuvenated by immune therapies, such as ICIs, to eliminate residual tumor cells. AG, tumor antigen; CSC, cancer stem cell; Tu, tumor.

"rescued" cells need to be maintained and fostered. To this end, another strategy has emerged for enhancing positive costimulatory pathways, such as CD40, OX40, or CD137, and providing cytokines, such as IL2, IL7, IL12, or IL15, for immune cell activation and expansion. Agonists for CD40 (CP-870,893), OX40 (MED16469), and CD137 (BMS 663519 and PF 05082566) are being investigated in clinical trials—some designed for patients with HNC. These agonists are frequently being used in combination with cetuximab or nivolumab in clinical trials based on the evidence that agonistic anti-CD137 mAbs potentiate T-cell antitumor functions and stimulate NK cell activity (48). It is worth noting that immune cells in the TME that coexpress stimulatory CD137 and inhibitory receptors such as PD-1 could be readily redirected toward activation pathways by immunotherapies (49). Toll-like receptor (TLR) agonists, such as TLR-8, induce maturation and cross-priming of DCs and upregulate NK-cell–dependent lysis of tumor cells in combination with cetuximab (50).

Adoptive Cell Therapy in HNC

Adoptive cell-based therapies (ACT) used for treatment of cancer involve transfer of *ex vivo* expanded tumor-reactive T cells into patients. Prior to transfer, cultured T cells can be modified or engineered to improve their *in vivo* antitumor activity. This form of immunotherapy has been infrequently used in HNC patients, because of limitations related to expansion of TA-specific T cells and the paucity in HNC of well-defined molecular targets that could be effectively used for engineering of T cells to increase their recruitment to tumors and boost their antitumor cytotoxicity. In an early phase I clinical trial for HNC patients with recurrent/metastatic HNC, 35% of patients who were treated with T cells controlled tumor growth (51). In a more recent trial, adoptive T-cell transfers after chemotherapy were performed in patients with resectable HNC, and the patients who received T cells had improved OS (52).

Cancer Stem Cells in HNC

Cancer stem cells (CSC) have been linked to treatment failure, resistance to therapy, recurrence, and metastasis (53). These small populations of highly tumorigenic, self-renewing, therapy-resistant cells are $CD44^{+}$, have high levels of active aldehyde dehydrogenase ($ALDH^{high}$), and are sensitive to immunotherapy with CSC-primed $CD8^{+}$ T cells *in vitro* and *in vivo* (54). These and other results from *in vivo* studies targeting stem cells in mice suggest that immunotherapy may be effective in eliminating this subset of chemotherapy-resistant tumorigenic cells (55).

Table 2. Key facts about HNCs and immune therapies

- HNCs evolve numerous ways of escape from the host immune system.
- The TME in HNC is strongly immunosuppressive.
- HNCs have high mutational activity.
- Immune profiles of HNC are heterogeneous.
- Immune therapies aim at rejuvenation of antitumor immunity.
- Responses to checkpoint inhibitors or other immune therapies have been limited.
- Combinations of immune therapies with conventional therapies are in clinical trials.
- Future immune therapies for HNC will be guided by immunogenetics and will be personalized.

Table 3. Future immunotherapy for HNC

1. Immunotherapy will be delivered in combination with conventional therapies (surgery, chemotherapy, and radiotherapy) to take advantage of the effects of conventional therapies on:
   a. Decrease in the tumor burden
   b. Elimination of suppressor cells
   c. Increased mutation rates
   d. Increased tumor vulnerability to immune cells
2. Different immunotherapeutic strategies for HNC subtypes with different viral (e.g., HPV^+ vs. HPV^-) or clinicopathologic presentations (e.g., "inflamed" vs. "noninflamed" tumors) will be rationally selected.
3. Personalized immunotherapy for HNC based on immunogenetics and advanced profiling technologies will become a standard of care:
   a. Full spectrum of genetic aberrations will be defined.
   b. Immune signatures of individual tumors will be established.
   c. Combined analysis of genetic/immunologic profiles will become routine.
   d. Biomarkers for predicting prognosis will be identified.
   e. Selection of optimal immune therapies will be facilitated from many available, including:
      - mAbs,
      - ICIs,
      - neoantigen-targeting vaccines,
      - cytokines,
      - stimulatory receptor agonists,
      - ACT,
      - small-molecule inhibitors,
      - oncolytic virotherapy, and
      - CSC inhibitors.
   f. Immune/molecular/genetic monitoring of clinical responses using noninvasive "liquid biopsies" (plasma DNA and exosomes) will become feasible.
   g. Biomarkers of outcome will be defined.

Future of Immunotherapy for HNC

After several years of initial experience with immunotherapy of HNC, it is possible to predict that within next few years, it will become fully integrated into the spectrum of conventional HNC therapies. Immune therapies emerge as nontoxic, highly specific, targeted treatments that can be used as monotherapies or in combination with conventional therapies or drugs that block tumor escape. Immunotherapies given to patients with HNC can ameliorate or restore compromised TA-specific immune responses and decrease/eliminate tumor-induced suppression of immune effector cells (Table 2). They can induce TA-specific memory responses that might be able to prevent tumor recurrence and provide long-term survival benefits. They are effective in silencing cancer stem cells. The limited beneficial effects of ICIs in HNC emphasize the fact that pervasive immune suppression is the major barrier to effective therapies in HNC. This has intensified the search for new actionable immune checkpoints within the TME of HNC and the development of new therapies that will be needed for more effective restoration of immune competence. HNC is a heterogeneous disease, encompassing HPV^+ and HPV^- cancers, among other clinicopathologic subtypes, all requiring distinct therapeutic approaches. Immunotherapy offering a wide variety of therapeutic strategies will be especially useful in meeting this need.

There are many challenges to making immunotherapy a standard of care in HNC. Foremost is the selection of immune therapy likely to benefit the patient. Extensive genetic, molecular, and immunologic evaluations of the TME in HNC (5, 56) suggest that immune therapies, although rational in view of the existing prevalent immune suppression in this cancer, will have to be carefully selected to fit with the suppression profile of each tumor and with the previous or concurrent therapy being administered to each patient (Table 3). No biomarkers are currently available to inform either the selection of therapy or outcome. It appears, however, that immunotherapy of HNC will be greatly facilitated by technical advances in the field of immunogenetics. Recent findings from deep sequencing of the HNC genome indicate that a large diversity of genetic alterations exist in these cancers (57). Most of these alterations seem to fall within a few major biological pathways, as if those pathways that best promote tumor growth are aberrantly activated via genetic alterations. Evidence exists, for example, that molecular signaling of *PIK3CA*, the most commonly mutated oncogene in HNC (58), is involved in regulating activity of the COX–PGE_2 pathway, the most immunoinhibitory molecular axis in the TME of HNC (17). In the near future, the ability to identify immune defects resulting from genetic aberrations in HNC will enable us to map the immunogenetic profiles of each HNC. This in turn will allow for profiling of specific immune dysfunctions in the TME and for selection of immune therapies that are likely to correct the existing defects. The ability to identify patients who can benefit from immune therapy will improve outcome. Furthermore, using WGS to identify point mutations or other genetic aberrations that can be recognized by T cells provides motivation for producing new vaccines that target neoantigens with high efficiency and are strongly immunogenic. Additional advantages will come from the discovery of novel biomarkers of outcome or response to therapy. Technologies are already available for establishing immune cell–specific signatures of tumors using gene microarrays, flow cytometry, RNA-Seq, and antibody-based protein arrays. The availability of these data will be critical in search for and validation of biomarkers of prognosis, response to therapy, or outcome. The development of simple blood tests for assessments of the mutational burden or for emergence of microsatellite instability (MSI) after chemotherapy is in progress (59) and will greatly facilitate linking of genetic alterations to changes in the specific molecular pathways signaling immune dysfunction. Overall, high mutational activity in HNCs bodes well for the application of immunogenetic approaches to personalize future immune therapies based upon silencing of the major immunosuppressive molecular pathways driven via the identified genetic alterations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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