Immunity in Head and Neck Cancer

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Abstract

Head and neck cancers are a diverse group of malignancies that includes an increasing number of virally mediated cancers in addition to tumors caused by tobacco and alcohol use. In both cases, tumor development is intimately related to the host immune system, and the status of an endogenous antitumor response is likely prognostic. Virally mediated cancers provide unique targets for preventive vaccines that generate immune responses directed against virus-associated antigens. Once head and neck tumors develop, they are commonly treated with surgery, radiotherapy, and/or chemotherapy. These treatments are associated with significant toxicities, and despite this, subgroups of patients respond poorly and are likely to relapse and die of their disease. Tumor immunotherapy may allow for improvements in both treatment-associated toxicity and outcome. In addition to providing specific targets for therapeutic vaccines and adoptive therapy, virally associated cancers may also be particularly dependent on immune checkpoints; therefore, immune checkpoint inhibitors are being actively tested for these diseases. Cancers that are not virally mediated may also respond to immunotherapies, and biomarkers that could predict response to immunotherapy irrespective of viral status are being evaluated. Multiple ongoing studies are testing benefits of immunotherapy in the management of metastatic squamous cell carcinoma of the head and neck. Early promising results pave the way for future studies that will expand testing to nonmetastatic diseases and other types of head and neck cancers. Prospects of combining various immunotherapies and more established treatments such as chemotherapy and radiotherapy are very intriguing and may provide synergistic benefits. Cancer Immunol Res; 3(1); 12–17. ©2015 AACR.

Introduction

Head and neck cancers are a diverse set of malignancies originating from the nasopharynx, oropharynx, larynx, hypopharynx, oral cavity, nasal cavity, paranasal sinuses, cervical lymph nodes, and salivary glands. These malignancies affect more than 50,000 people per year in the United States and half a million people across the world, placing them approximately sixth in global incidence (1, 2). Squamous cell carcinoma (SCC) is the most common histology, although other tumor types such as adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid cancers also arise in this region.

Tobacco and alcohol use is the predominant risk factor for the development of carcinomas across all subsites of the head and neck; however, oncogenic viruses also play a large and increasingly important role in tumor development. Infection with the Epstein–Barr virus (EBV) has long been appreciated as a cause of endemic nasopharyngeal cancer (3). In addition, over the past few decades, developed countries such as the United States have experienced an epidemic of oropharyngeal cancers associated with oral infection with human papillomavirus type 16 (HPV-16; ref. 1).

The increasing incidence of HPV-associated cancers has placed renewed emphasis on improving head and neck cancer outcomes and reducing treatment-associated toxicity. Treatment of head and neck cancers is challenging for many reasons, including the variety of histologies and range of behaviors among cancers, as well as the anatomical complexity of the head and neck region. Tumors are generally located in close proximity or within structures that are vital to speaking, swallowing, and breathing, and local treatment approaches delicately balance efforts to maximize control with organ preservation in an attempt to preserve long-term quality of life.

Because of these complex local control issues, treatment for patients with head and neck cancer often requires multimodality care, including a combination of surgery, chemotherapy, and radiotherapy. Biologic therapy with cetuximab, an antibody that inhibits the epidermal growth factor receptor (EGFR), also has a proven role for patients with both localized and metastatic disease (4, 5). Despite the significant advances in head and neck cancer treatment in recent decades with more refined surgical techniques such as transoral robotic surgery (TORS), targeted biologic agents such as cetuximab, and more precise intensity-modulated radiation (IMRT), there is still much work to be done to improve outcomes for patients with head and neck cancer. As mentioned above, the incidence of HPV-associated oropharyngeal cancer is rising to epidemic proportions. These cancers have a more favorable prognosis (6); however, serious side effects can linger and cause significant morbidity following treatment. In contrast, tobacco- and alcohol-associated cancers have a much more unfavorable prognosis, with approximately 50% of patients developing recurrent or metastatic disease (6). In the metastatic setting, despite the use of more aggressive treatment regimens, including chemotherapy in combination with cetuximab, outcomes remain poor, with median survival generally less than 1 year (5).

Tumor immunotherapy is a promising novel therapeutic strategy that may help improve both long-term toxicities and disease control rates. In tumors with a favorable prognosis, the use of

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tumor immunotherapy may facilitate treatment deintensification by serving as a substitute in place of toxic chemotherapy and/or radiotherapy. In contrast, for tumors that are more likely to recur, the use of immunotherapy in combination with established treatments could increase control rates. In this Crossroads overview, the immunologic landscape of head and neck cancers is discussed, along with the rationale for using tumor immunotherapy in this disease. The immune system plays an important role in head and neck carcinogenesis and tumor prevention. The status of the immune system is also likely to have prognostic value in patients with head and neck cancer. Finally, early data have illustrated the promise of tumor immunotherapy in head and neck cancer treatment.

Tumor Development

The immune system likely shapes the development of all head and neck malignancies, but its role is perhaps most clear in virally mediated cancers such as HPV-associated oropharyngeal tumors and EBV-associated nasopharyngeal cancers. Multiple lines of evidence support a causative association between HPV subtype 16 infection and oropharyngeal cancer and between EBV infection and nasopharyngeal cancer, including evidence of infection preceding the development of these cancers and identification of HPV/EBV DNA within tumor tissue (3, 7, 8). The mucosal immune system of the head and neck includes the lingual and palatine tonsils as well as adenoid and other lymphoid tissues within the nasopharynx. Discontinuity of reticulated epithelium in branched crypts located in these areas allows for sampling of the respiratory and oral microenvironment (9). EBV infection is very common and spreads from person to person via contact with infected saliva. Although the exact means by which oral HPV infection is transmitted remains under study, sexual practices likely have an important role. Recent data suggest that the prevalence of oncogenic HPV infection in the head and neck may be as high as 1%, with a bimodal incidence highest in early adulthood and then again in people in their early 60s (10). Assuming sexual behaviors that lead to transmission of the virus are most common in early adulthood, this second peak in incidence may represent reactivation of the virus that coincides with waning immunity.

Both EBV and oral HPV infection are not uncommon; however, nasopharyngeal and oropharyngeal cancers develop much more rarely. Failure of the immune system to clear these oncogenic infections likely places only a relative minority of infected individuals at higher risk of malignancy. The persistence of EBV or HPV infection in lymphoid tissue in the head and neck may be related to self-regulatory mechanisms that allow these tissues to sample the oral environment without leading to constant immune activation. To this end, the immune checkpoint ligand programmed cell death (PD)-L1 has been identified in tonsillar crypts irrespective of HPV infection, and PD-1^{+}–infiltrating lymphocytes are found in both chronic tonsillitis and HPV-associated oropharyngeal tumors (11). Once HPV infection is established, multiple immune inhibitory mechanisms, including activation of the PD-1/PD-L1 axis, may contribute to T-cell dysfunction and exhaustion, as in other types of chronic viral infections (12). Head and neck cancers not associated with HPV infection likely also co-opt immune regulatory mechanisms to facilitate their progression. Increased PD-L1 expression similarly has been detected on tobacco- and alcohol-induced SCCs of the head

and neck (11, 13–16), as well as other virally mediated tumors, including nasopharyngeal carcinoma and natural killer T (NKT)-cell lymphoma (17).

HPV-targeted vaccination is recommended for adolescent boys and girls to prevent incident HPV infection. Two different vaccine formulations are currently in use. The bivalent vaccine protects against the most prevalent oncogenic subtypes (HPV-16 and HPV-18) and the quadrivalent vaccine protects against subtypes 6 and 11. Both vaccines have proven roles in preventing gynecologic HPV infection, and recent evidence suggests that vaccination is at least equally effective in reducing the prevalence of oral infection (18). HPV-associated head and neck cancers likely take decades to develop after initial HPV infection; thus, data establishing vaccine efficacy in reducing the incidence of HPV-associated head and neck malignancies will take even longer to mature.

Premalignant lesions may be immunogenic and targetable with immunologic therapies to prevent progression to malignancy. Increased PD-L1 expression has been demonstrated on actinic chelitis, a premalignant condition of the oral cavity (14), as well as respiratory papilloma, lesions that can progress into larynx cancers (19). Although not necessarily indicative of a premalignant condition, a systemic antibody response directed against the oncogenic HPV E6 and E7 proteins has been demonstrated to be highly specific for the eventual diagnosis of oropharyngeal cancer (8). This includes antibody responses that predate oropharyngeal cancer diagnosis by many years. These antibody titers could be used to identify those at highest risk for inclusion in surveillance protocols. Similarly, IgA antibody responses directed against EBV antigens have also been investigated for their ability to aid in the diagnosis of nasopharyngeal cancers (20).

Immune Reactivity and Prognosis

Immunosuppressed patients are more likely to develop head and neck cancers (21), and tumors that occur in these individuals tend to be poorly responsive. This worse prognosis has been identified in multiple studies evaluating patients following solid organ as well as hematopoietic stem cell transplantation (22, 23).

Once head and neck cancers have developed, an endogenous host immune response is prognostic, as has been demonstrated for multiple tumor types (24). T-cell infiltration of both CD4^{+} and CD8^{+} populations were found to be prognostic in tonsillar and base of tongue SCCs (25, 26). Lymph node–infiltrating CD8^{+} T cells as well as CD20^{+} B cells were also found to be prognostic in both oropharyngeal and hypopharyngeal cancers, although interestingly, infiltration of T cells into the primary disease was not found to be prognostic in this cohort (27). In oral cavity cancers, peritumoral CD8^{+} T cells were found to be associated with lymph node metastases, tumor size, and clinical stage (13).

Expression of immune checkpoint ligands and their receptors has also been associated with prognosis in some instances, although the data are mixed. One study identified PD-1^{+}–infiltrating T cells as a favorable prognostic factor in HPV-associated oropharyngeal cancer (28). In other studies of patients with cancers of the oral cavity and oropharynx, PD-L1 expression was not prognostic (13), or was indicative of distant metastases but not local recurrence or overall survival (16).

The clearance of oncogenic viruses is also associated with outcome in virally induced malignancies. Circulating EBV DNA is prognostic when quantified both before and after definitive

treatment (29, 30), and there are plans to use DNA titers following definitive chemoradiation to help better select patients for adjuvant chemotherapy following definitive chemoradiation in an upcoming cooperative group study (31). Similarly, a recent evaluation of patients with HPV-associated oropharyngeal cancer demonstrates that the majority of those successfully treated no longer harbor evidence of oral infection approximately 1 year following treatment (32).

Immunotherapy as Treatment for Head and Neck Cancers

A plethora of immunotherapies are under active investigation for the treatment of established head and neck malignancies. These include vaccine approaches, adoptive T-cell therapy, and the use of targeted agents such as immune checkpoint inhibitors. An exhaustive summary of this promising area is beyond the scope of this Crossroads article, but some illustrative examples are described below.

The potential use of vaccination to prevent virally induced head and neck malignancies has been described above; however, tumor vaccines that treat established disease are also in development. The bivalent and quadrivalent HPV vaccines are directed against proteins that mediate viral entry into cells and are therefore not expected to be efficacious in preventing head and neck cancers following initial infection. However, virally mediated cancers such as HPV-associated oropharyngeal cancers do express unique targets such as the oncogenic E6 and E7 proteins that can be exploited by vaccination strategies. Unlike many other potential vaccine targets, these proteins are exogenous; consequently, it may be easier to overcome immune tolerance and generate an antitumor immune response. Moreover, any immune reaction directed against these antigens would be expected to spare normal host tissue. These virally associated oncogenic proteins tend to be relatively conserved across individual cancers given their importance in oncogenesis (in the case of E6 and E7, inhibition of p53 and pRb, respectively). This relative conservation in epitopes is in contrast with the more variable and pleiotropic mutations that are present in oncogenes in nonvirally driven malignancies.

Early data suggest that targeting E6 and E7 with vaccine-based approaches is feasible and efficacious. A phase I study attempted to combine HPV-16–derived peptides with the melanoma differentiation antigen MAGE-A3 into a therapeutic vaccine (33). Although there were no clinical responses in this small study, immune responses directed against the HPV epitopes targeted by the vaccine were detected, including T-cell responses in 4 of 5 treated patients. An additional preclinical study demonstrated the feasibility of inserting the E7 gene within a viral plasmid in a DNA-based HPV-targeting vaccine (34). Vaccines targeting HPV are also being explored for a range of premalignant and malignant gynecologic diseases, and these findings could potentially be applicable to HPV-associated head and neck cancers (35). Vaccination strategies are also being tested in HPV-negative malignancies; preliminary testing of a dendritic cell vaccine targeting p53 epitopes was reported recently (36).

T-cell–mediated immunotherapy also is an attractive strategy for virally induced cancers. Adoptive T-cell therapy directed against EBV antigens has met with some success for the treatment of EBV-mediated posttransplant lymphoproliferative disorders

(PTLD; ref. 37). Unfortunately, as compared with PTLD, EBV-associated nasopharyngeal cancers express fewer Epstein–Barr nuclear antigens (EBNA) and have lower overall immunogenicity. Consequently, strategies that target-specific antigens that are more often expressed such as LMP1-2 and EBNA1 may be the most efficacious (37, 38). Preliminary studies have shown the feasibility of adoptive T-cell therapy directed against HPV-16 by demonstrating the ability of the transferred T cells to reactivate and expand E6/E7-specific T cells from more than 60% of oropharyngeal cancer patients tested (39).

Transfer of T cells with engineered chimeric antigen receptors (CAR T cells) has been explored in multiple tumor types and could be used in the treatment of head and neck cancers. Although data specific for head and neck cancers are currently limited, T cells can be engineered with specificity for EGFR. EGFR is expressed on 90% of head and neck cancers, and cetuximab, the monoclonal antibody targeting EGFR, has a demonstrated survival benefit in head and neck malignancies (4, 5). Although potentially effective, CAR T cells with too great an affinity for EGFR could have detrimental side effects given the widespread expression of EGFR (40).

Immunotherapies that activate an otherwise dormant immune response are directed toward immune-activating ligands and checkpoint inhibitors. Toll-like receptor ligands could potentially enhance immune activation and have been tested in combination with cetuximab for head and neck malignancies, with promising results in animal models (41). Inhibitors of the immune checkpoint receptors CTLA-4 and PD-1, as well as PD-L1 inhibitors, are being actively tested. As described above, expression of PD-L1 has been identified on multiple types of head and neck tumors, and expression of this PD-1 ligand may be predictive of a response to treatments that inhibit the PD-1 axis (42). Preliminary results from 60 patients with metastatic head and neck cancers enrolled in the phase Ib KEYNOTE study evaluating the PD-1 inhibitor pembrolizumab in multiple malignancy types were presented recently (43). This study required participants to have tumors that demonstrated expression of PD-L1. With limited follow-up, there were no serious drug-related adverse events, and responses were noted in patients with both HPV-associated and non–HPV-related tumors. Decreased tumor burden was reported in 51% of evaluable patients, and a 20% response rate based on RECIST criteria. Interestingly, patients who had tumors that demonstrated the most robust PD-L1 expression were also the patients most likely to respond to treatment (46% response rate as compared with 11%). Similarly, Segal and colleagues (44) have presented promising preliminary results from patients with metastatic head and neck cancers treated in a multiarm dose expansion study with the PD-L1 inhibitor MEDI4736. These 54 patients were not preselected on the basis of PD-L1 expression. MEDI4736 was well tolerated with no adverse effects leading to discontinuation of the study drug. There was a 14% response rate, with another 18% of patients demonstrating stable disease. Among the subset of patients with PD-L1–expressing tumors, the response rate was 50%.

Summary and Future Directions

The crossroads between tumor immunology and head and neck cancer highlights the important advancements that have been made in our understanding of the immunity in head and neck malignancy, ongoing investigations in this area, and promising
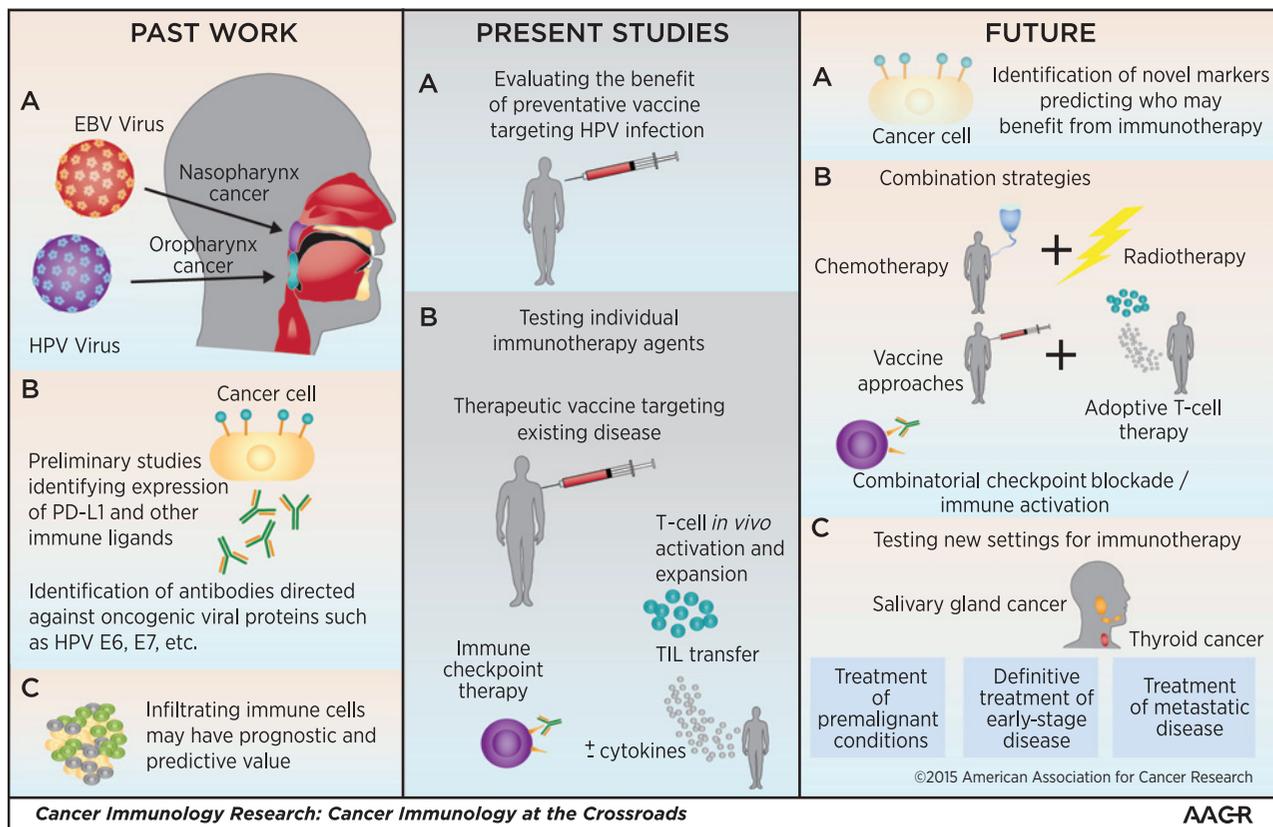
Cancer Immunology Research: Cancer Immunology at the Crossroads

Figure 1.
The past, present, and future of the crossroads between tumor immunotherapy and the treatment of head and neck cancers. Past, previous work has (A) established the role of the oncogenic viruses EBV and HPV in tumor development within the nasopharynx and oropharynx, respectively; (B) identified immunologic markers on head and neck tumors and circulating antibodies targeting viral antigens; and (C) suggested that immune markers may be prognostic and predictive of response to traditional therapies. Present, ongoing work is (A) establishing the benefit of preventative vaccines; and (B) actively testing a variety of individual immunotherapy strategies, including therapeutic vaccination, adoptive T-cell therapy, and immune checkpoint blockade. Future, promising strategies include (A) determining markers that predict who will benefit from immunotherapy; (B) combination strategies exploiting potential synergies between immunotherapies and radiotherapy or chemotherapy; and (C) expanding the settings and malignancies for which immunotherapy is used.

areas for future research (Fig. 1). The immune system has an important role in the development of head and neck cancers. Endogenous immune responses generated against these malignancies and the expression of immunologic markers may be prognostic and could help guide treatment strategies. Finally, tumor immunotherapy ranging from preventive vaccination against virally mediated cancers to the use of PD-1 checkpoint inhibitors for the treatment of metastatic disease has shown significant promise.

Future investigations will seek to establish the benefit of tumor immunotherapy in the prevention and treatment of head and neck cancers and to expand the indications for this approach. On the basis of the promising early results of PD-1 inhibition in patients with metastatic disease, larger phase II and phase III clinical trials evaluating efficacy are in progress. It remains to be seen whether PD-1 or PD-L1 inhibition will be more effective in this regard; this may depend on the relative importance of other PD-1 ligands such as PD-L2 and cross-talk between PD-L1 and other receptors yet to be determined (45). Similarly, the relevance of other potential immunologic checkpoint and immune-activating receptors such as OX40, Tim3, and Lag-3 remains unknown. Inhibition or activation of multiple immunologic pathways important to head and neck cancers may ultimately provide more

significant and durable benefit than inhibition of a single receptor such as PD-1.

Additional work is needed to better define the patient population that will benefit from immunologic therapies and to expand this population to encompass more than a minority of patients. Preliminary data for PD-1 inhibition in head and neck cancer appear to support the use of PD-L1 expression as a predictive marker (43, 44); however, PD-L1 expression may be prognostic irrespective of the administration of immune therapy. Regardless, the threshold of PD-L1 expression that best predicts response is still unknown. Complicating things further, PD-L1 expression is dynamic and potentially could change in response to tumor growth or evolution of the tumor microenvironment. Different patterns of PD-L1 expression have been identified in head and neck cancers, and the significance of this remains unknown (11).

If PD-L1 expression is confirmed as predictive of response to PD-1 blockade in head and neck cancers, then the plasticity of its expression also represents an opportunity to increase the number of patients who may respond to immunologic therapy. More broadly speaking, combination strategies may increase the percentage of patients that respond to tumor immunotherapy. Traditional cancer treatments such as

radiotherapy and chemotherapy may be immunogenic and could potentially synergize with tumor immunotherapy or increase the number of responding patients (46). Cetuximab may also work via immunologic mechanisms such as NK cell–mediated antibody-dependent cytotoxicity (41), and may therefore work well in combination with tumor immunotherapy approaches.

Although immunotherapies are being tested most actively for patients with metastatic squamous cell cancers of the head and neck, they could be expanded to other settings and a diverse array of head and neck cancers. In the first-line setting, immunotherapy could be used in combination with traditional therapies for treatment intensification in patients with a high risk of recurrence. Indeed, a trial combining CTLA-4 inhibition with ipilimumab with definitive cetuximab radiation is ongoing (NCT01935921). In contrast, patients with favorable-risk HPV-associated disease could be treated with immunotherapy as part of a treatment deintensification strategy. This could allow for a reduction in the use of traditional therapies such as chemotherapy and radiotherapy that are associated with long-term side effects that adversely affect quality of life. Finally, certain subgroups of patients with head and neck cancers, such as those with primary salivary gland, thyroid, and skin tumors, have few options for effective systemic therapies. Treatment regimens for these tumors are often extrapolated from studies conducted in patients with mucosal SCCs, with generally poor results in the metastatic setting. These tumors may be prime candidates for immunotherapeutic approaches.

In conclusion, increased understanding of tumor immunology has helped the oncology community begin to realize the promise of cancer immunotherapy. In parallel, the epidemiology and treatment of head and neck cancers has undergone a rapid evolution with an increasing understanding of the epidemic of virally mediated disease and the use of more sophisticated treatments, such as TORS, IMRT, and biologically targeted agents. There is much work to be done to integrate these developments to advance head and neck cancer therapy beyond the crossroads.

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