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Modulation of Therapeutic Sensitivity by Human Papillomavirus

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Abstract

Human papillomaviruses (HPVs) are small double-stranded DNA viruses that pose significant public health concerns as the causative agent of approximately 5% of worldwide cancers. The HPV oncogenes E6 and E7 play key roles in carcinogenesis. In the last 15 years there has been a significant increase in the incidence of HPV-related head and neck cancers arising primarily in the oropharynx. Patients with HPV-positive head and neck cancers (HNCs) have a significantly improved prognosis compared to those with HPV-negative disease. In this review we will discuss data suggesting how HPV oncogenes modulate both the intrinsic radiation sensitivity of HNCs and also have important effects upon the tumor microenvironment. Together, these findings contribute to the improved outcomes seen in patients with HPV-positive HNC.

Introduction

Early viral discovery efforts by Shope and Hurst described an agent that could be transmitted from one animal to another, was of a defined size that enabled it to be filtered, caused the growth of benign papillomas, and ultimately resulted in the identification of the papillomavirus family [1]. This discovery of human papillomavirus (HPV) in 1956, led to the finding that this pathogen causes unrestrained epithelial proliferations including papillomas, warts, condylomas, and carcinomas [2]. During the second half of the 20th century, HPV has subsequently been shown to be the cause of squamous cell carcinomas (SCCs) arising in multiple anatomic locations including the squamous epithelium of the uterine cervix, vulva, vagina, penis, anal canal, and head and neck (in particular the oropharynx). Radiation plays a key role in the curative treatment of each of these cancers and growing evidence suggests that the function of the papillomavirus proteins may play an important role in the relative increased sensitivity of these cancers to radiation, via the modulation of DNA damage response and alteration of the tumor microenvironment. Herein,

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we briefly review the role of HPV in cancer development and describe work by a number of groups to elucidate mechanisms underlying the significantly improved outcomes seen in patients with HPV-positive tumors.

Human papillomavirus and carcinogenesis

The HPV genome encodes approximately 8,000 base pairs of double-stranded DNA. The virus is non-enveloped and different viral subtypes are classified on the basis of their L1 capsid protein into nearly 200 unique subtypes (see http://pave.niaid.nih.gov/ for the most current listing). HPVs can be sub-classified into cutaneous or mucosal subtypes based on their specific tissue tropism [3] or can be separated into low-risk and high-risk types based on their ability to cause malignant transformation and induce cancer. The high risk subtypes (Table 1) can cause cancers of the uterine cervix, anus, vagina, vulva, penis, and head and neck [4].

The viral proteins encoded by the HPV genome (Fig. 1) regulate the viral life cycle [5]. The viral capsid proteins L1 and L2 play no known role in carcinogenesis but are the immunologic targets of current HPV vaccines such as Gardasil or Cervarix; in the tumor cells of many HPV-associated cancers expression of these proteins is lost, thus limiting the value of these vaccines for cancer treatment [6]. Viral genome replication is controlled by the early genes E1 and E2 which also regulate the transcription of other viral genes [5]. A splice variant of the E1^E4 mRNA transcript encodes the E4 protein which facilitates viral particle release and may play a role in G2 arrest [7]. Most important to the clinical oncologist, three HPV oncogenes, E5, E6, and E7 drive unrestrained cellular proliferation to as a required feature of viral amplification but also play key roles in carcinogenesis by promoting proliferation and inducing genomic instability [8–10].

The E7 protein enhances proliferation of HPV-infected cells by targeting members of the pocket protein family for degradation, most notably retinoblastoma 1 (Rb) [9, 11]. Rb plays an important role in preventing excessive cell growth by inhibiting cell cycle progression [12]. A higher avidity interaction between high-risk E7 and Rb appears to promote Rb's degradation in the more oncogenic HPV subtypes [9]. Acting alone, E7-driven proliferation can result in a p53-dependent anti-proliferative response. This function is countered by HPV E6 mediated degradation of p53 via activation of the ubiquitin ligase E6AP [8, 13]. E6 and E7 act in concert to inhibit apoptosis, promote unrestrained cell proliferation, and play key roles in the promotion of genomic instability [2, 8, 14, 15], all critical factors in HPV-mediated carcinogenesis. E6 and E7 cooperate to promote chromosomal segregation errors and aneuploidy [15] while E7 induces centrosome synthesis via CDK2 activity [16]. Beyond these historically well-described functions, it is now clear that both E6 and E7 interact with a multitude of additional cellular proteins that may play additional roles in carcinogenesis [17, 18]. Finally, while much less is known about its function, E5 can cooperate with E6 and E7 and plays a minor role in transformation [10].

HPV AS AN INDICATOR OF TREATMENT RESPONSE

As cervical cancer is overwhelmingly associated with HPV positivity, it is difficult to assess the role of the viral oncoproteins in contrast to non-viral associated malignancies in that

setting. The mixed etiology of head and neck cancer (HNC), however, provides an opportunity to study the influence of HPV on clinical outcomes. HPV-status is now a well-accepted prognostic biomarker in HNC and appears to have similar value in anal cancer [19–22]. Two recent meta-analyses by O'Rorke and Petrelli both confirm a remarkable survival advantage for patients with HPV-positive HNC as compared to those with HPV-negative disease (HR 0.46; 95% CI, 0.37–0.57 and HR = 0.33; 95% CI, 0.27–0.40, respectively) [23, 24]. Tobacco abuse appears to be a modifying factor as patients with HPV-positive HNC and significant tobacco abuse histories have outcomes intermediate to those in HPV-positive non-smokers or traditional HPV-negative (i.e. tobacco and/or alcohol associated) HNCs [25–28]. Due to these differences, clinical trials in HNC currently stratify patients on the basis of HPV status (including tobacco use) or are designed specifically for HPV-positive or HPV-negative patients. Ongoing efforts in HNC are focused on decreasing the intensity of therapy while maintaining excellent cure rates (see [29]) and may provide important insights that can be later applied to other HPV-associated malignancies.

HPV and RADIATION SENSITIVITY

Since being first postulated [30], evidence has grown that enhanced sensitivity to radiation in HPV-positive HNC is an important contributor to the improved prognosis of these patients [31]. A number of both epidemiological and mechanistic hypotheses have been proposed to explain the improved outcomes consistently seen in HPV-positive HNC patients. One of the simplest is that patients with HPV-positive HNC are typically younger and healthier than those with HPV-negative disease [25, 32, 33]. This makes them better able to tolerate therapy and less likely to die from comorbid illnesses. While this may be true, even within well-matched cohorts of patients (i.e. similar age, performance status, and disease stage), those with HPV-positive cancers have significantly improved outcomes compared to those with HPV-negative disease.

Over the last few years, we and others have demonstrated that both HPV-16 positive HNC cell lines [34–37] and oral epithelial cells engineered to express the HPV-16 E6 oncoprotein [34, 38], have greater intrinsic sensitivity to radiation (i.e. lower survival fractions over a range of radiation doses) than HPV-negative cells. While to date only a limited number of trials have reported outcomes comparing HPV+ and HPV− patients treated with radiation monotherapy, in these reports, tumor HPV status was highly prognostic for improved local control and overall survival [39, 40]. This result is consistent with increased intrinsic sensitivity to radiation demonstrated in the lab in cell line and mouse studies. Several complementary mechanisms appear to be at work to explain these profound differences. Following radiation, residual wild-type p53 not yet degraded by HPV-E6 activates a canonical p53 transcriptional program resulting in cell cycle arrest and apoptosis [34, 36]. HPV-positive tumors also exhibit impaired double-strand break repair capacity that may influence radiosensitivity [35, 41] that may be related to p16-mediated impairment of homologous recombination-mediated DNA repair [37]. A finding common to several of these studies is a profound and sustained G2 arrest induced by radiation in HPV positive tumors [34–37].

A number of other factors also likely play a role in the improved outcomes seen in patients with HPV-positive HNC. For example, in the DAHANCA 5 trial, HPV-negative tumors demonstrated a larger benefit to hypoxic modification than HPV-positive tumors, a finding that correlated with an increase in hypoxia markers in HPV-negative tumors [42, 43]. This data led to the hypothesis that increased hypoxia in HPV-negative tumors may be partially responsible for the differential in response to radiation compared to less hypoxic HPV-positive tumors. The hypoxia/HPV link remains unsettled, however, as contrasting data from several other groups has failed to demonstrate any correlation between imaging markers of hypoxia and HPV status [44, 45]. It may be that the increased radiation sensitivity seen in HPV-positive HNCs compensates for the presence of hypoxia in these tumors at current radiation doses, but that as radiation doses are decreased the impact of hypoxia will again become evident. In fact, work by Sorensen et al has demonstrated that HPV-positive cells demonstrate a similar oxygen enhancement ratio as HPV-negative cells [46].

An increasing body of evidence suggests that HPV-positive tumors may provide a more immunologically rich environment that may also affect tumor control. Tumor infiltrating T cells are increased in HPV-positive tumors [47–50], and are shifted from naïve to memory or effector T cells with greater frequency compared to patients with HPV-negative tumors [51]. Similarly, programmed death-1 (PD-1) positive tumor infiltrating lymphocytes are more common in HPV-positive tumors [52]. Several groups have also reported the detection of circulating anti-HPV16 antibodies and circulating and tumor-infiltrating HPV-specific T cells in patients with HPV-positive HNC, a finding that is correlated with improved clinical outcome [53–55]. In fact, Ward and colleagues found that patients with HPV-positive tumors with high levels of tumor infiltrating lymphocytes have increased survival compared to patients with HPV-positive tumors with low levels of tumor infiltrating lymphocytes (3-yr DSS 96% vs. 59%), a group which had a similar prognosis as patients with HPV-negative tumors [56].

Potentially necessary for the development of cancer in this more robust immune environment, HPV-positive tumors have also been reported to employ several immune evasion strategies. HPV-positive cancers exhibit impaired immune effector recognition and block immune-mediated cell death via reduction of HLA and FasL expression, promote an immune suppressive cytokine milieu, and recruit immunosuppressive regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages [49, 53, 57–59].

It has been hypothesized that radiation disrupts this tolerogenic phenotype, essentially “reawakening” the immune response against HPV-positive tumors. Radiation increases the percentage of activated circulating CD8+ and CD4+ lymphocytes, a finding that correlates with improved survival [60, 61]. Further data supporting an important role for the immune system in HPV-positive cancers comes from in vivo studies by Spanos and colleagues who demonstrated that control of HPV-positive mouse tumors with radiation was significantly better than that of HPV-negative tumors, but only in the presence of an intact immune system in the animals [62]. In addition, low-dose radiation therapy has been found to greatly enhance the antitumor response to DNA vaccination in E7-expressing tumor-bearing mice, with increased frequency of peripheral and infiltrating E7-specific CD8+ T cells, enhanced tumor cell susceptibility to CTL-mediated lysis, and improved survival of mice treated with

vaccination and radiation therapy compared to either therapy alone [63]. Several clinical studies are poised to provide much needed evidence regarding the role of the immune response in HPV-positive cancers and how radiation may promote immune-mediated tumor clearance.

CONCLUSIONS

HPV has been a growing cause of HNC. While current treatment for patients with HPV-associated disease does not differ from those with HPV-negative cancers, it is likely that ongoing clinical trials will soon provide data to guide the personalization of treatment based on HPV-status of their cancers. A growing body of basic and translational studies describe a mechanistic basis for the improved outcomes seen in HPV-positive patients and point to key roles for microenvironmental differences in therapeutic response. Additional details that emerge over the coming years will further define the molecular underpinnings of HPV-mediated altered radiation sensitivity and how HPV effects on the tumor microenvironment can be used to personalize therapy for these patients. Better understanding of these mechanisms will ultimately enhance the efficacy of radiation in the treatment of these cancers.

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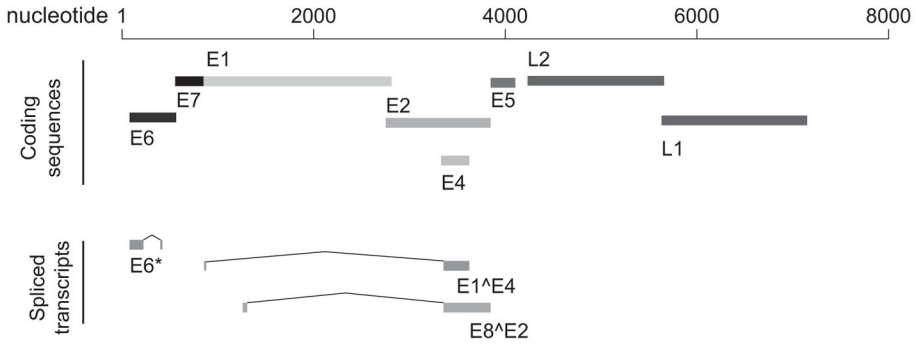

Figure 1. HPV-16

HPV-16 is a 7905 bp genome that encodes eight proteins and at least 11 mRNA transcripts. E6 and E7 are the primary HPV oncogenes and play critical roles in oncogenesis via their interactions with the cellular proteins p53 and RB, among others.

Table 1

Association of HPV subtypes with mucosal or skin carcinomas.

	Category	HPV types
Mucosal	Group 1: Carcinogenic to humans	16, 18, 31, 33, 45, 51, 52
	Group 2A: Probably carcinogenic to humans	68
	Group 2B: Possiblity carcinogenic to humans	26, 53, 64, 65, 66, 67, 69, 70, 73, 82
	Carcinomas of Skin	5, 8; less commonly 14, 17, 20, 47