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Review

Molecular mechanisms of human papillomavirus-related carcinogenesis in head and neck cancer

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Abstract

This review examines the general cellular and molecular underpinnings of human papillomavirus (HPV)-related carcinogenesis in the context of head and neck squamous cell carcinoma (HNSCC) and focuses on HPV-positive oropharyngeal squamous cell carcinoma in areas for which specific data is available. It covers the major pathways dysregulated in HPV-positive HNSCC and the genome-wide changes associated with this disease.

Keywords: HNSCC; Squamous cell carcinoma; Oropharyngeal; HPV; Viral integration; Chromatin

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) encompasses a heterogeneous group of malignant neoplasms arising from the non-keratinizing epithelium of the upper aerodigestive tract. Anatomic subsites of HNSCC include the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. Squamous cell carcinoma arising from these subsites collectively represents the sixth most common malignancy worldwide, accounting for 932,000 new cases and 379,000 deaths in 2015 [1].

Over the past four decades, striking epidemiological trends have been observed in HNSCC. Although the overall incidence of HNSCC has declined slightly, the relative contribution of each anatomic subsite to the overall incidence of HNSCC has shifted dramatically [2]. Incidence rates of tumors arising from non-oropharyngeal subsites (oral cavity, hypopharynx and larynx) have decreased while the incidence of oropharyngeal squamous cell carcinoma has steadily grown [3]. These subsite-specific epidemiological trends have been attributed to shifts in societal factors that have resulted in changes in exposure to two divergent, but complementary classes of HNSCC risk factors: (1) tobacco and alcohol consumption and (2) human papillomavirus (HPV) infection. Successful public health campaigns in high-income countries are largely credited with achieving population-level decreases in tobacco and alcohol consumption [4] with concomitant declines in tobacco-associated tumors such as non-oropharyngeal HNSCC and lung cancer [5]. Trends toward sexual practices that increase the risk of contracting sexually transmitted pathogens, like HPV, have been linked to the rise in HPV-associated cancers including oropharyngeal HNSCC (OPSCC) and anal cancers [5,6]. Currently, HPV-positive OPSCC cases are surpassing the incidence of HPV-positive cervical cancer [3,7].

Human papillomavirus is the most common sexually transmitted infection in the United States and the primary infectious cause of HNSCC [8,9]. Although the spread of high-risk HPV infection is pervasive, the virus is cleared by

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most people within 18 months [10]. It is believed that persistent infection is necessary for the development of HPV-associated malignancies. The oropharynx exhibits the strongest relationship to HPV. Indeed, HPV-positive oropharyngeal squamous cell carcinoma (OPSCC), is recognized as a distinct neoplastic entity with a unique molecular, histopathological, epidemiological, and clinical profile [11–13]. Patients with HPV-positive OPSCC diverge from the classical profile of HNSCC patients in that they are more often younger than 60 years in age and less likely to report a history of heavy tobacco and alcohol consumption [12]. HPV-positive OPSCC also exhibits marked sensitivity to treatment and a significantly better prognosis than HPV-negative HNSCC [11], observations which have led to the establishment of a staging system specific to this entity [14] and shifts in treatment paradigms [15]. These distinct epidemiological and clinical features are manifestations of the unique underlying biology of HPV-positive OPSCC. However, much of the research into the role of HPV in HNSCC was conducted before intimate links between HPV and OPSCC were widely recognized.

2. Human papillomavirus

Papillomaviridae is an ancient clade of non-enveloped viruses with a circular double-stranded DNA genome [16]. Within this family, approximately 200 human papillomavirus genotypes, or 'types', have been described based on viral genome sequence [17]. Twelve HPV types have been defined by the WHO as high-risk and exhibit high oncogenic potential [18]. At least 10 of these oncogenic HPV types (HPV16, 18, 31, 33, 45, 51, 52, 56, 58, and 59), as well as 6 low-risk HPV types (11, 32, 44, 53, 57, and 81), have been isolated from HNSCC tumors [19–23]. HPV16 represents the primary viral cause of HNSCC and is identified in at least 87% of HPV-positive OPSCC [24]. HPV18 and HPV33, the next most prevalent types, account for most of the remainder of HPV-positive HNSCC [24].

All papillomaviruses possess a genome of approximately 8 kilobases encoding 8 open reading frames (ORFs) that enable viral genome replication and viral particle assembly (Fig. 1). ORFs of the HPV genome are organized based on the timing of expression with respect to the viral life cycle: early (E1, E2, E4, E5, E6, and E7) and late (L1 and L2) genes [25]. The E1 viral helicase and E2 DNA-binding protein directly mediate viral genome replication, while E4, E5, E6, and E7 are accessory proteins that coordinate viral genome amplification and virulence. The late genes L1 and L2 encode viral capsid proteins necessary for the final stages of virion assembly and mediate viral entry into future host cells. The functional diversity of this limited set of ORFs is expanded through complex patterns of viral transcript splicing and stage-specific gene expression that is linked to host cell differentiation [26].

2.1. Infection

The host cells for HPV infection are keratinocyte progenitors located in the basal layer of stratified squamous epithelia and adhered to the epithelial basement membrane. Experimental models suggest that infection requires viral access to the basement membrane [27] (Fig. 2). In the epidermis and anogenital tract, HPV gains access to basal cells through micro-abrasions that occur during sexual or other direct physical contact [28].

In the oropharynx, HPV infection may occur in the absence of epithelial abrasion. The palatine, lingual, tubal, and adenoid tonsils are lymphoid structures collectively known as Waldeyer's tonsillar ring. Constituents of Waldeyer's ring possess a specialized reticulated squamous epithelium infiltrated with lymphoid tissue. The reticulated epithelium contains a fenestrated, discontinuous basement membrane thought to allow immune cells access to oral antigens [29]. These fenestrations also represent natural interruptions in epithelial barriers that likely provide HPV access to basal keratinocytes in the absence of traumatic epithelial disruption (Fig. 2) [30]. Indeed, the unique epithelial properties of Waldeyer's ring may explain the disproportionate tendency of HPV to cause squamous cell carcinoma of the palatine and lingual tonsils [31].

Upon reaching the basal keratinocyte, HPV preferentially binds components of the extracellular matrix. The L1 capsid protein directly engages basement membrane heparin sulfate proteoglycans [32], triggering conformational changes in L1 and L2 that transfer virion particles to host cellular uptake receptor(s) necessary for viral internalization. Although cellular HPV receptors mediating viral entry have not been definitively identified, accumulating evidence suggests that tetraspanin-enriched microdomains on the plasma membrane serve as the primary platform for viral entry into the cell [33]. Once internalized, virion particles undergo endosomal transport, uncoating, and cellular sorting into the nucleus [34].

Upon entry and uncoating, the circular viral DNA is transported to the nucleus where it exists as an episome, a genetic element separate from the host cell genome, that employs host cell enzymes to replicate its genome along with host chromosomes and is maintained at low-copy number (~50–100 copies per cell) [35]. Tight regulation of low-copy replication of the viral genome in basal keratinocytes serves as one mechanism by which HPV evades the host immune system. Oncoproteins E6 and E7 are expressed prior to productive viral replication, driving cell cycle entry and cell proliferation in the basal and parabasal cells [26]. In oncogenic HPV genotypes, cell cycle dysregulation by E6 and E7 constitutes the initial steps driving HPV-related carcinogenesis.

The expression of viral genes and virion production increases rapidly in daughter keratinocyte progenitors undergoing differentiation and progressing toward the mucosal surface [36]. In normal stratified squamous epithelia, only basal keratinocyte stem cells possess the potential to proliferate. Asymmetric cell division of these keratinocyte stem cells leads to two daughter cells: one renewed basal stem cell and one cell destined to become a terminally-differentiated keratinocyte. HPV-encoded genes perturb key keratinocyte differentiation and proliferation pathways to favor virus production and viral life cycle completion. In high-risk HPV types, these perturbations predispose cells to neoplastic transformation.