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Review

Human papillomaviruses and cancer

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ABSTRACT

Human papillomaviruses (HPV) are small oncogenic DNA viruses of which more than 200 types have been identified to date. A small subset of these is etiologically linked to the development of anogenital malignancies such as cervical cancer. In addition, recent studies established a causative relationship between these high-risk HPV types and tonsillar and oropharyngeal cancer. Clinical management of cervical cancer and head and neck squamous cell carcinomas (HNSCCs) is largely standardized and involves surgical removal of the tumor tissue as well as adjuvant chemoradiation therapy. Notably, the response to therapeutic intervention of HPV-positive HNSCCs has been found to be better as compared to HPV-negative tumors. Although the existing HPV vaccine is solely licensed for the prevention of cervical cancer, it might also have prophylactic potential for the development of high-risk HPV-associated HNSCCs. Another group of viruses, which belongs to the beta-HPV subgroup, has been implicated in nonmelanoma skin cancer, however, the etiology remains to be established. Treatment of HPV-induced nonmelanoma skin cancer is based on local excision. However, topically applied immune-modulating substances represent non-surgical alternatives for the management of smaller cutaneous tumors. In this review we present the current knowledge of the role of HPV in cancer development and discuss clinical management options as well as targets for the development of future intervention therapies.

Papillomaviruses (PVs) are commonly known to cause benign papillomas as well as epithelial malignancies. PVs are small non-enveloped viruses with a diameter of approximately 55 nm and a double-stranded circular DNA genome comprising almost 8000 nucleotide base pairs. The genome is arranged into the upstream regulatory region (URR) and nine to ten open reading frames (ORFs) encoding the viral early and late genes. Late gene expression produces the structural proteins L1 and L2, which assemble into the viral capsid structure, whereas early gene activity translates into the regulatory proteins E1–E8. PVs generally infect keratinocytes within the basal layer of stratified epithelia by gaining access through wounds within the skin and mucosa. Initial attachment to the cell surface has largely been attributed to rely on heparan sulfate proteoglycans [36]. Subsequent conformational changes within L2 result in furin-dependent cleavage of its N-terminal sequence [65]. The current model of cellular entry involves a novel actin-dependent, but clathrin-, cavoelin-, cholesterol- and dynamin-independent pathway related to macropinocytosis [20,71]. Woodham et al. suggest a ligand-induced mechanism in which pre-entry binding of the capsid proteins to integrins may activate signaling cascades that recruit the annexin A2 heterodimer to the cell membrane, which then facilitates internalization of the virus [84]. Viral entry and posterior replication are largely contingent on keratinocyte differentiation.

Human papillomaviruses (HPV) are classified depending on their tissue tropism. Alpha-HPVs infect mucosal tissue whereas beta-, gamma-, nu- and mu-subtypes infect cutaneous sites [17] (see http://pave.niaid.nih.gov for detailed phylogeny). In addition, mucosal HPVs are distinguished by their potential to cause malignant progression. Low-risk HPVs include HPV 6, 11, 40, 42, 43, 44 54, 61, 70, 72 and 81 [62] which can cause low-grade lesions such as condylomas and benign cervical lesions and are rarely found in malignancies [83]. High-risk HPVs including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 gained notoriety by being the primary causative agents of cervical carcinoma [14,72].

Alpha-HPV-associated cancer development and therapy

Each year, 0.5 million new cases of cervical cancer are reported with 274,000 associated deaths worldwide [5]. Certain high-risk HPV types, recognized as class I carcinogens by the World Health Organization, are necessary risk factors for the development of cervical cancer [14,39,72]. Early stages (I–IIa) of cervical cancer can be

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treated rather successfully, but locally advanced cancers are characterized by high recurrence rates and a poor prognosis. The standard therapy of locally advanced cervical cancer is a combination of radiotherapy and cisplatin-based chemotherapy with an overall 5-year survival of less than 50%. Patients with stage IV or recurrent cervical cancer treated with cisplatin alone or in combination with topotecan only have a median survival of less than one year [57]. Despite widespread screening for cervical cancer, this disease continues to claim large numbers of lives, particularly among medically underserved populations of women. In addition to cervical carcinoma, high-risk HPVs were found in 26% of head and neck squamous cell carcinomas (HNSCCs) despite the main risk factors being tobacco, alcohol, poor oral hygiene and genetic pre-disposition [44]. It has previously been shown that patients suffering from alcohol- or tobacco-induced HNSCC are at reduced risk of simultaneously contracting HPV-based HNSCC [4,15]. This may be explained by a recent finding that increased levels of the annexin A2 ligand, secretory leukocyte protease inhibitor (SLPI), are typical for tumors induced by smoking [28]. High expression of SLPI in turn inhibits annexin A2, which is essential for viral entry into the host cell [84].

Within the heterogeneous group of HNSCCs, almost 70% of all tonsillar and oropharyngeal carcinoma cases are HPV-positive in economically developed countries [43,52,66]. Regardless of this knowledge there is no screening routine available in order to detect early HPV lesions in the tonsils and oropharynx. Clinical management is largely standardized across the HPV-positive and -negative tumor types and stages of progression. Treatment of stage I and II oropharyngeal cancers usually involves surgery accompanied by radiotherapy. More locally advanced cancers are surgically removed and treated by chemoradiation therapy [51]. It is generally accepted that HPV-positive HNSCCs have a significantly better prognosis as compared to HPV-negative tumors. Patients with HPV-positive tumor status who do not consume tobacco or alcohol presented with a reportedly higher survival rate probably due to increased sensitivity to chemo- and radiotherapy [52]. Several studies show that young individuals seem to be at greater risk for developing HPV-positive tonsillar or oropharyngeal cancers [11,27], with one study reporting a higher percentage of cases in young men [27]. The young age of the risk group may be a result of changes in sexual behavior such as earlier onset of sexual activity and increased oral practices. These patients also exert better responses to intervention therapy and have fewer recurrences as compared to age-matched patients with HPV-negative HNSCCs [52].

Since 2006 two recombinant vaccines against human papillomavirus types 6, 11, 16, and 18 are available. Although this is an important step in the battle against cervical cancer, the viral types for which these vaccines provide protection are responsible for only 70% of the cases of cervical cancer [39]. However, it has been shown that the vaccines confer cross protection against HPV types 31, 45 and 52 (reviewed by [6]). It is worth noting that in more than 95% of HPV-positive tonsillar and oropharygeal cancers the high-risk types HPV 16 and 18 were detected [44] and a prophylactic vaccine regime may be the key in preventing HPV-based head and neck cancers. Currently there are no data available evaluating the efficacy of HPV-vaccination for preventing oral cancers. Even though vaccination may prevent HPV-associated cancers, previous assumption was that it will provide no protection for individuals who already have been exposed to high-risk HPV types. However, recent research demonstrates a 67% efficacy of the quadrivalent vaccine Gardasil® in seropositive, but HPV DNA-negative women aged 24–45 years [10]. Nevertheless, the need for significant advances in the diagnosis and treatment of HPV-dependent cancers will persist.

By better understanding the course of high-risk HPV infection, new approaches for clinical management of both cervical carcinoma and HNSCCs may be discovered. The normal productive PV life cycle is tightly linked to keratinocyte differentiation where the genome undergoes episomal replication generating infectious viral particles. Persistent infection with high-risk types, however, may lead to the integration of viral DNA into the host cell genome, which is accompanied by a deletion of the genes encoding the viral replication regulators E1 and E2. The expression of E2 proteins has been described to repress the transcription of the viral oncogenes E6 and E7 [21]. Therefore, loss of the E2 region during integration may lead to the constitutive activation of both oncogenes thereby fostering carcinogenesis. However, recent reports demonstrate that in approximately 35% of cervical cancer patients full-length viral genomes are present and actively transcribed raising the possibility of E2-expression in addition to E6 and E7-proteins within cervical cancer cells [40,50]. E6 and E7 of HPV16 and 18 interact with a large number of host cell proteins in order to manipulate cell proliferation, senescence and apoptosis (Fig. 1). The E6-proteins of high-risk HPV interact with the p53 tumor suppressor and induce its proteolytic degradation [70]. In addition, HPV 16 E6-protein has been shown to induce telomerase activity [41]. Both functions as well as E6-induced transcriptional changes in HPV-positive cells were reported to be dependent on the ubiquitin-ligase E6-associated protein (E6AP) [69]. Finally, E6-proteins of high-risk HPVs share a conserved C-terminal domain, which mediates its interaction with PDZ (PSD-95, Dlg, Zo-1) domain-containing proteins such as hDlg [38,48], MAGI-1 [26], hScrib [63], MUPP1 [47] and PTPN3 [35] which are involved in epithelial cell polarity [54,59]. E7 interacts with the retinoblastoma-family tumor suppressor proteins pRb [24,61,73], p107 [46] as well as p130 [16] and disrupts their interaction with E2F transcription factors, resulting in the activation of E2F-dependent gene expression and cell cycle progression [7,53,56]. One of the proteins up-regulated upon pRb degradation is p16, which is encoded by the sequence of the CDKN2a gene [37]. An accumulation of p16 was reported in HPV-positive cancers and serves as a prognostic marker for intervention therapy responses [42,55]. Expression of E6 and E7 transcripts is controlled by both cellular and viral transcription factors. Interestingly, E6 and E7 also act as potent mitotic mutators, thereby increasing the occurrence of mutations that contribute to carcinogenic progression (reviewed in [54]). These multiple interactions with important cellular pathways of the host cell may represent potential targets for developing specific therapeutic alternatives for HPV-based cancer treatment. Other intervention therapy approaches may arise from the fact that normal cells and tumor cells markedly differ in their energy metabolism. When glucose is metabolized in normal cells in the presence of adequate oxygen, the process results in complete oxidation of glucose and involves cytoplasmic glycolysis as well as mitochondrial citric acid cycle and electron transport chain/oxidative phosphorylation. In contrast, tumor cells rely mostly on the conversion of glucose into lactate rather than mitochondrial oxidation for energy production. The mitochondrial function is suppressed in most tumor cells even though oxygen is available [33]. In agreement with these findings in virally transformed cells, HPV-induced oncogenic transformation of cervical epithelium is associated with increased expression of the glucose transporter GLUT1 [67]. Some studies have shown that more aggressive tumors have a greater demand for metabolic energy and hence for glucose. Accordingly, the expression level of GLUT1 correlates reciprocally with the survival of cancer patients [82]. A recent study has demonstrated a role for the sodium-coupled glucose transporter SGLT1 in epithelial cancers [82]. The levels of SGLT1 protein and its transport activity are elevated in malignant epithelial cell lines by the co-expression of EGFR, which stabilizes SGLT1 within the membrane. Overexpression of EGFR is frequent in cervical cancer cells [25] as well as HPV-positive head and neck tumors [45], providing a basis for exploiting the EGF