

THE ROLE OF HUMAN PAPILLOMAVIRUSES IN HUMAN CANCERS

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Virus-Host Interaction
4. Association of HPVs with human cancers
 - 4.1. Squamous cell carcinomas of the cervix and related cancers
 - 4.2. Squamous cell carcinoma of the upper respiratory tract and the oral cavity
 - 4.3. Epidermodysplasia verruciformis and non-melanoma skin cancers
5. HPV oncogenes and initiation of carcinogenesis
 - 5.1. Induction of DNA synthesis
 - 5.2. Abrogation of the cellular p53 response
 - 5.3. Abrogation of telomere erosion
6. HPV E6 and E7 and malignant progression
7. Concluding Remarks
8. Acknowledgments
9. References

1. ABSTRACT

Of the more than 100 different human papillomavirus types (HPVs), the “high-risk” HPVs are associated with the vast majority of cervical carcinoma, and a pathologically distinct group of oropharyngeal tumors. In addition, other HPVs are associated with cutaneous tumors, in particular epidermodysplasia verruciformis and non-melanoma skin cancers. In general, HPV-associated cancers arise from a single accidental integration event of the viral genome into a host cell chromosome. Integration is a terminal event for the viral life cycle. Even though integration does not occur at specific chromosomal hot spots in the human genome, it follows a consistent pattern with respect to the viral genome, and expression of the HPV E6 and E7 genes is consistently retained. The normal function of E6 and E7 is to establish and maintain a cellular milieu that allows for viral genome replication. E6 and E7 target important cellular growth regulatory circuits among them the p53 and retinoblastoma tumor suppressors, respectively. Uncontrolled expression of the E6 and E7 proteins, as a consequence of viral integration is paramount to the establishment and maintenance of the tumorigenic state. In addition, expression of E6 and E7 increases genomic instability of the host cell thus accelerating malignant progression. Taken together, there is compelling molecular and epidemiological evidence in support of an oncogenic function of certain HPVs.

2. INTRODUCTION

Papillomaviruses are a family of small DNA viruses. Their circular double-stranded DNA genomes of

less than 8,000 base pairs are packaged into non-enveloped particles of approximately 55 nm. They show a marked preference for infection of epithelial cells and have been isolated from in a wide range of hosts, including humans. Papillomaviruses are exquisitely species-specific and cross-species transmission of the virus is very rare. In addition, there is also a preference for the site of infection; some HPVs preferentially infect cutaneous epithelia, whereas another group of HPVs targets mucosal epithelia (reviewed in 1).

Papillomavirus genomes have a very simple organization, and can be separated into three portions, two coding regions and a non-coding regulatory region. The open reading frames are denoted E (for “early”) and L (for “late”) followed by a number according to their coding potential. The lowest numbers denotes the longest; the highest number the shortest open reading frame. The major blocks of coding sequence are all contained on a single strand of the genome, are overlapping and encoded within all three possible reading frames. The early region encodes approximately 8 open reading frames all of which fulfill regulatory functions necessary for the viral conquest of the host cell and vital to the production of progeny virus. As a consequence of complex splicing patterns, some early mRNAs contain coding information derived from more than one open reading frame (reviewed in 2). The late genes encode the viral capsid proteins. Certain early genes such as E2, E4 and possibly others, also play important roles during the late phase of these viruses (3-5). The regulatory region of the papillomaviruses (denoted as the long control region LCR, upstream regulatory region URR,

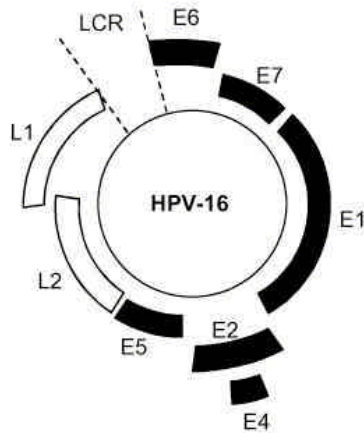


Figure 1. Schematic structure of the HPV-16 genome. Early genes encoding viral regulatory proteins are indicated by black boxes. Transcription of these genes is through sequences in the Long Control Region (LCR) that also contains viral origin of replication. The two genes in the late region encode viral capsid proteins and are indicated by open boxes. See text for details and references.

or non-coding region NCR) does not specify major open reading frames but contains the origin of viral DNA replication, and a large number of binding sites for cellular and papillomaviral transcription factors that act in concert as an enhanceosome (6). A schematic depiction of the HPV-16 genome is shown in figure 1.

3. VIRUS-HOST INTERACTION

As obligatory intracellular parasites, papillomaviruses need to coerce the host epithelial cell for their survival and replication. With the exception of the viral E1 and E2 genes, which in concert act as a viral origin of replication binding complex with helicase and ATPase activity (7-9), HPVs rely on the host machinery for synthesizing their genomes. An additional complication arises from the specificity of these viruses to replicate in squamous epithelia. Initial infection of papillomaviruses is through basal cells, a single layer of undifferentiated proliferating cells normally protected by several layers of non-dividing differentiated cells. Access to basal cells is achieved through small abrasions caused by various forms of physical trauma. In addition basal-like cells are also readily accessible at squamo-columnar junctions such as the transformation zone in the cervix (reviewed in 10). The precise steps of the viral entry process remain enigmatic but it has been shown that some human papillomavirus particles interact with integrin structures that specifically decorate such cells (11). In addition papillomavirus infection requires heparan sulfate at the cell surface (12).

It is presumed that in some cases papillomaviruses can retain their genomes at low copy number in basal-like cells for extended periods of time without causing a clinically overt lesion. It is possible that such “viral latency” only occurs upon infection of specific cells with stem-cell like properties, and it is not clear whether the clinical prognosis of this type of infection is

different from those that give rise to more immediately productive and clinically apparent lesions.

Papillomaviruses are non-lytic viruses that are transmitted as cargoes within differentiated epithelial squames that are constantly shed by the infected host. Viral genome amplification and packaging of progeny virus occurs in terminally differentiated strata of the infected epithelium. The cells in these layers are normally devoid of DNA synthesis machinery because they have terminally withdrawn from the cell division cycle and are therefore intrinsically incapable to support viral genome production. Hence a vital endeavor of the viral replication strategy is to guarantee that differentiated cells retain cellular milieu that can biochemically support viral replication. Since several other elements of the viral life cycle such as induction of a viral replication mode that can rapidly generate a large number of papillomavirus genomes per cell, as well as the switch to late gene expression are all thought to be hard-wired to the cellular differentiation program, the viral replication strategy is not to globally interfere with the differentiation program of its epithelial host cell. Instead, papillomaviruses have developed a replication strategy that uncouples cellular differentiation and proliferation (reviewed in 13). This yields the benign hyperproliferative epithelial lesions that are referred to as warts and are caused by productive viral replication. When the replication process goes awry, however, this viral replication strategy can bring great harm to the host and cause lesions that have an inherent potential to progress to malignant invasive carcinomas.

Much remains to be learned about the viral life cycle and the intricate interplay of viral proteins with host factors, as it has proven difficult to establish tissue culture systems that fully recapitulate the life cycle of papillomaviruses. In recent years several systems have been established (14, 15) and these will yield much important information on these subjects.

4. ASSOCIATION OF HPVs WITH HUMAN CANCERS

The list of human papillomaviruses (HPVs) that have been identified from a variety of epithelial tissues has grown to include more than 100 different types. At one time or another most humans have been infected with HPV and it has been suggested that HPVs may be a component of the common microflora of human epithelia (16). The ubiquity of these viruses underlines the inherent complexity of establishing a conclusive link between HPV infection and the etiology of human tumors. Most HPVs cause benign hyperplastic lesions, warts, that have little or no probability for malignant progression. These HPVs are designated low-risk HPVs. In contrast, a small group of high-risk HPVs cause lesions that can undergo malignant progression. A comprehensive examination of the available data by the International Agency of Research on Cancer and the World Health Organization in 1995 led to the classification of HPV-16 and HPV-18 as human carcinogens (17). These and other high-risk HPVs are detected in almost 100% of cervical cancers (18) with

HPV-associated cancer

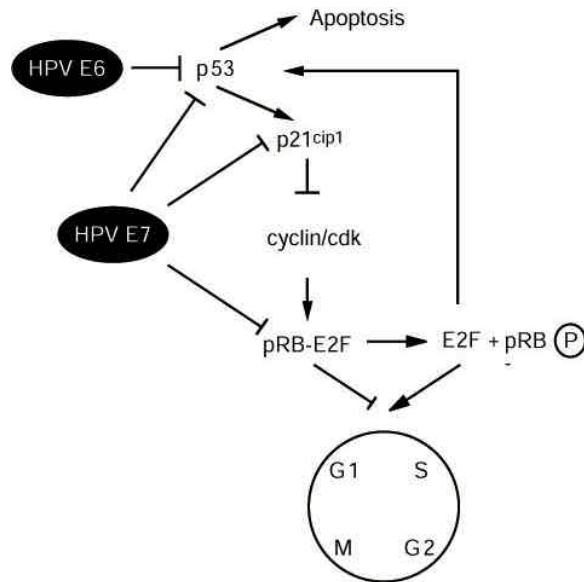


Figure 2. Functional abrogation of the p53 and pRB tumor suppressor pathways as a result of high-risk HPV E6/E7 expression in cervical carcinoma cells. See text for details and references.

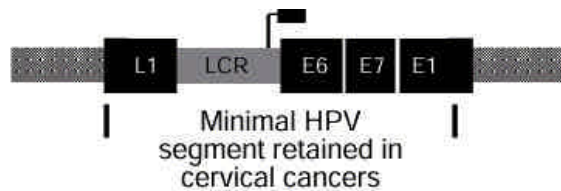


Figure 3. Schematic structure of the minimal region of the HPV genome retained after integration. The LCR and the E6/E7 regions are regularly retained and expressed in cervical cancers. Due to integration, expression of E6/E7 escapes regulation by the viral E2 protein, which is regularly deleted or mutated. See text for details and references.

regular retention of expression of the viral E6 and E7 genes. In addition to epidemiological data, the oncogenic function of high-risk HPVs is substantiated by a large number of compelling molecular studies performed in tissue culture and transgenic animal models. These genes score as oncogenes in a number of standard tissue culture assays.

Nevertheless, high-risk HPV associated lesions have a relatively low incidence of malignant progression. It is estimated that a high-risk HPV infected patient has a less than one in thirty lifetime risk to develop cervical cancer. Malignant progression often occurs in conjunction with other risk factors such as decreased immune function, or after a long latency period after other genomic alterations in the host cell DNA have occurred (see figure 2) (reviewed in 10).

4.1. Squamous cell carcinomas of the cervix and related cancers

A subgroup of approximately 30 HPVs preferentially infects mucosal epithelia and these HPVs

have been classified as high-risk and low-risk depending on the potential for malignant progression of the lesions that they cause. Low-risk HPVs (HPV-6 and HPV-11) cause genital warts (condyloma acuminata) and were directly cloned from such lesions. In contrast, high-risk HPVs cause cervical intraepithelial neoplasia (CIN), a premalignant lesion with a certain risk for malignant progression to cervical carcinoma. High-risk HPV genomes were directly cloned from cervical carcinoma. Cervical cancers generally represent non-productive infections and no progeny virus is produced. This is a consequence of the integration of the viral genome into the host chromosome. In the majority of all cases only fragments of viral genomes are retained (figure 3). However, the viral sequences are regularly transcribed, and HPV derived RNAs are detected in the tumors. Integration of the viral genome is a hallmark of malignant progression, and most tumors contain at least some integrated HPV copies (reviewed in 19). Although integration does not target specific hot spots in the host chromosome, it follows a specific pattern with respect to the viral genome. In addition to viral enhancer sequences, only two HPV genes, E6 and E7 are consistently maintained. In addition, there is a strong selection for integration events that result in the deletion of the viral E2 transcription factor. E2 encodes a DNA binding protein that in complex with the DNA helicase E1 can interact with the viral origin sequence. In addition, E2 homodimers interact with specific sequences in the viral control region and act as DNA binding repressors of viral gene transcription (reviewed in 20, 21). Abrogation of E2 expression as a consequence of integration leads to dysregulated E6 and E7 expression and is thought to directly contribute to malignant progression. Consistent with this notion, re-expression of E2 in cervical cancer cells lines leads to decreased E6 and E7 expression, functional re-activation of the tumor suppressor pathways targeted by the viral oncoproteins, and reversal of the tumorigenic phenotype (22, 23).

Malignant progression a high-risk HPV associated lesion can occur a long time after the initial infection event and in addition to viral integration, cellular changes need to occur that further accelerate malignant progression. The high-risk HPV E6 and E7 proteins have the capacity to induce genomic instability (24) even when expressed from viral episomes and low copy number (25). Therefore, expression of these genes greatly enhances the propensity for genetic alterations to occur that may permit tumorigenic conversion. In addition, even the integration process may be at least in part driven by the ability of E6 and E7 to induce genomic instability (26).

The frequently slow progression of a premalignant lesion to a frank carcinoma provides for an extended a window of opportunity to recognize and clinically manage high-risk HPV-associated lesions. Widespread use of the Papanicolaou smear ("Pap smear"), a simple cytological examination of stained exfoliated cervical cells has dramatically decreased the incidence rate of cervical cancer. This strikingly illustrates the impact of early detection on cancer prevention. In countries where this screen is not routinely performed, cervical cancer

HPV-associated cancer

remains the leading cause of cancer death in young women and accounts for up to 25% of all cancers in females. Nearly 500,000 new cases of cervical cancer occur per annum worldwide making it the third most frequent cancer in women (27, 28). In the United States approximately 13,500 of new cervical carcinoma cases are diagnosed each year often in medically underserved segments of the population, causing a death toll of nearly 5,000 mostly young women.

Transmission of these HPVs is by sexual contact and consequently the incidence of precancerous cervical lesions and cervical cancer is strongly correlated to early onset of sexual activity and the number of lifetime sex partners. The cervical squamo-columnar transformation zone is particularly susceptible to HPV infection. This may be because at these locations basal-like squamous epithelial cells are uniquely accessible for infection. Alternatively the cervical squamo-columnar transformation zone may harbor a specific cell type that when high-risk HPV infected is uniquely vulnerable to malignant progression.

The male counterparts to CIN are penile intraepithelial lesions (PIN). They generally occur at a much lower rate than CIN, but are highly associated with high-risk HPV infections and can undergo malignant progression to penile carcinoma. The lower incidence of PIN versus CIN is not understood, but in general the incidence-rates of cervical and penile carcinoma are correlated in many parts of the world. In addition, high-risk HPV infections are also highly associated with several other squamous cell carcinomas that arise in the anogenital tract including vulvar and perianal carcinomas (reviewed in 10).

4.2. Squamous cell carcinoma of the upper respiratory tract and the oral cavity

Most oral tumors arise in individuals with a long-term history of alcohol and tobacco abuse (reviewed in 29). However, recent molecular epidemiological studies have revealed that approximately 25% of oral carcinomas are associated with high-risk HPV infections (30). Oropharyngeal and tonsillar carcinomas are particularly highly associated with HPVs, and HPV positive tumors occur more likely in younger patients who do not have some of the classical risk factors. The mode of transmission has not been definitively determined (31). Additional studies are also necessary to more clearly define possible precursor lesions and screening programs that may aid in the early detection of premalignant lesions.

4.3. Epidermodysplasia verruciformis and non-melanoma skin cancers

Epidermodysplasia verruciformis (EV) is an exceedingly rare skin disease that is first manifested in early childhood by reddish flat wart-like cutaneous lesions. At a certain rate they progress to frank carcinomas and a substantial fraction of EV patients eventually go on to develop skin cancers. This disease provided an early indication that HPVs may contribute to human tumors. A family of cutaneous HPVs, different from those detected in anogenital and oral tumors, have been isolated from such

lesions. Among these, HPV-5 and HPV-8 have been studied in greatest detail (32). Molecular studies have shown that like in cervical cancer the cutaneous HPVs are transcriptionally active in the lesions but the oncogenic potential of the viral gene products has not been extensively studied. A co-carcinogenic function of ultraviolet radiation has been postulated based on observations that malignant progression preferentially takes place in sun-exposed areas of the body. EV also has a clear genetic component (33), and impaired cell-mediated immunity significantly increases the risk for malignant progression. The fact that EV frequently occurs in immune suppressed patients provides additional support to the idea that weakened immune function contributes to progression (reviewed in 34).

More recently, a large group of HPV-5 and HPV-8 related cutaneous HPVs have also been isolated from non-melanoma skin cancers in both immune-suppressed and immune-competent patients but whether these viruses directly contribute to the genesis of these tumors is debated (35).

5. HPV ONCOGENES AND INITIATION OF CARCINOGENESIS

One of the most consistent hallmarks of carcinogenic progression is the physical integration of the HPV genome into the host cell DNA. As a consequence, in addition to the viral regulatory region, less than 1000 base pairs of HPV coding sequence is minimally retained and transcribed in a tumor (figure 3). These retained HPV sequences encode two low molecular weight viral proteins, E6 and E7. Continued expression of E6 and E7 is necessary not only for the induction but also for the maintenance of the transformed state.

Expression of E6 and E7 in normal human epithelial cells causes their immortalization (36, 37). When grown under conditions that allow for the formation of a stratified epithelial structure, HPV E6/E7 expressing cells display histopathological features typical of high-risk HPV associated precancerous lesions (38). Ablation of E6 and/or E7 expression by a variety of methods caused dramatic detrimental effects on the growth of HPV positive cancer cell lines that been in culture for several decades (23, 39-41). Moreover, HPV E6/E7 expressing cells have a dramatically decreased ability to maintain the integrity of their genomes (24). HPV E7 in particular may provide a mutator function through its propensity to induce centrosome-associated mitotic abnormalities that lead to aneuploidy and enhance the likelihood for malignant progression (42).

Even though other HPV genes may also contribute to the oncogenic potential of high-risk HPVs, the following discussion will be focused on E6 and E7 and their main cellular targets. Detailed contemporary reviews on the biological activities, biochemical properties and cellular targets of E6 and/or E7 have been published (1, 43, 44) and should be consulted for a more detailed description of the biochemical properties of E6 and E7.

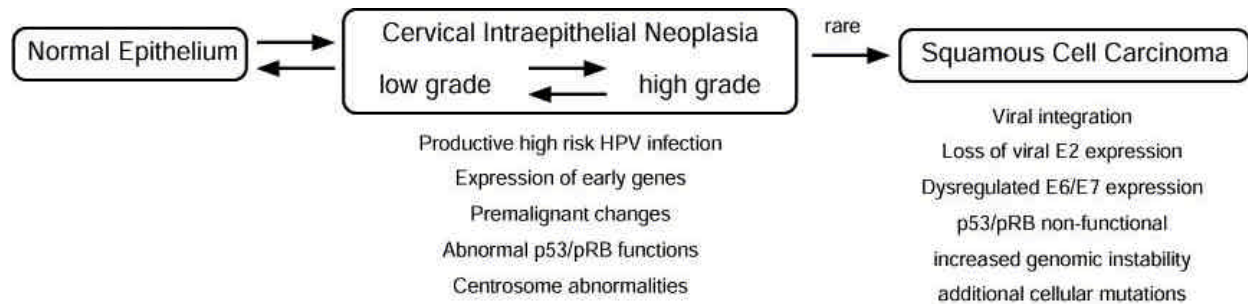


Figure 4. Pathological manifestations of high-risk HPV infections and malignant progression in the anogenital tract epithelium. Many infections with high-risk HPVs remain clinically inconspicuous or cause low-grade cervical intraepithelial lesions that frequently regress. Progression to high-grade lesions does occur, but these may still regress. Progression to cervical carcinoma is a rare event that is commonly caused by the accidental integration of the viral DNA into the host cell chromosome, leading to dysregulated E6 and E7 oncogene expression. See text for details and references.

5.1. Induction of DNA Synthesis

The paramount objective of the virus is subvert the host cell to ensure genome replication in terminally differentiated cells that have permanently withdrawn from the cell division cycle. Studies with epithelial raft cultures revealed that HPV E7 expression could induce differentiated cells to undergo DNA synthesis (45). High-risk HPV E7 scores as an oncogene in a number of transformation assays (reviewed in 43). The E7 protein can interact with the retinoblastoma tumor suppressor protein pRB (46), an important negative regulator of entry into the DNA synthesis (S) phase of the cell division cycle. It shares this ability with oncoproteins encoded by other small DNA tumor viruses, including the large tumor antigens of many polyomaviruses (47) and the adenovirus E1A oncoproteins (48). Each of these proteins contains a related amino acid sequence motif, the LXCXE domain that serves as the core pRB interaction domain in each of three viral proteins. Low-risk HPV E7 proteins can also interact with pRB, albeit at a reduced efficiency (49). However, efficient pRB binding is not a unique identifier of high-risk HPV encoded E7 proteins and does not strictly correlate with cellular transformation. The E7 protein encoded by low-risk cutaneous HPV-1a can interact with pRB as efficiently as the high-risk HPV-16 E7 protein, yet unlike HPV-16 E7 does not transform tissue culture cells (50, 51). However, high-risk HPV proteins have the unique ability to induce the proteolytic degradation of pRB (52), an activity not shared by other pRB binding viral oncoproteins or low-risk mucosal or HPV-1 E7 proteins (53). A mutational analysis revealed that the oncogenic activity of HPV-16 E7 is closely related to its ability to induce pRB degradation (53, 54).

The retinoblastoma tumor suppressor is a negative regulator of the G1/S transition. In addition pRB is also involved in the regulation of apoptosis and cellular differentiation. The growth inhibitory activity is an important aspect of the tumor suppressor function of pRB and has been studied in great detail. The RB gene encodes a 105 to 110 kD nuclear phosphoprotein whose activity is regulated cyclical phosphorylation/dephosphorylation through the sequential action of cdk4/cyclin D or cdk6/cyclin D complexes in G1, cdk2/cyclin E and

cdk2/cyclin A complexes in early and late S phase, respectively, followed by dephosphorylation towards the end of mitosis (reviewed in 55). The phosphorylation state governs the association with other cellular proteins, most notably E2F transcription factor family members (reviewed in 56). E2F transcription factors regulate expression of many factors that are rate limiting for DNA replication and cell division. When bound to pRB (or p107 and p130, two related members of the pRB family that are also targeted by the viral oncoproteins) E2Fs act as transcriptional repressors and S phase entry is blocked. Phosphorylation of pRB in G1 results in the disruption of pRB/E2F complexes and free E2F is now able to induce expression of S-phase specific genes (reviewed in 57).

In high-risk HPV expressing the steady state levels of hypophosphorylated pRB are much decreased due to E7-mediated degradation, and the remaining hypophosphorylated pRB is mostly bound to E7 and, hence, unable to interact with E2F, resulting in the disruption of an important regulatory node that limits S-phase entry in normal cells (figure 4).

5.2. Abrogation of the cellular p53 response

Aberrant S-phase entry is sensed by a cellular surveillance and defense mechanism that involves the tumor suppressor p53. As with pRB, p53 function is abrogated in the majority of human tumors. The p53 protein is a DNA-binding transcription factor with a short half-life. The rapid turnover is through proteasomal degradation mediated by the ubiquitin ligase mdm2. Activation in response to aberrant DNA synthesis and other forms of “cellular stress” including DNA damage and hypoxia induces posttranslational modifications that decrease the ability of mdm2 to target p53 to degradation. Consequently the cellular steady state levels increase resulting in the increased expression of p53-responsive genes. Higher expression of such genes enforces a cell cycle arrest or induces an apoptotic response (reviewed in 58).

In keeping with this model, it has been demonstrated that high-risk HPV E7-expressing cells contain increased p53 levels (59) and that they are

predisposed to undergo apoptosis through a pathway that is at least in part p53-dependent (54, 60) (figure 4). To thwart such a cellular p53 response during viral DNA replication, high-risk HPVs have developed multiple strategies to inactivate p53 function. The HPV E6 protein can interact with and reprogram the ubiquitin ligase E6-AP (61, 62) to induce p53 multiubiquitination, thereby further accelerating the proteasomal degradation of p53 (63). As a consequence, E6 expressing cells contain very low levels of p53 (63, 64), and most importantly, as E6/E6-AP mediated p53 degradation appears to be less susceptible to post-translational p53 modifications that hamper degradation through mdm2, p53 levels do not increase in response to "cellular stress" signals (figure 4). In addition there is evidence that suggests that the remaining p53 in high-risk HPV positive cells may be transcriptionally impotent and E7 can interfere with the transcriptional activity of p53 (65, 66).

The combined functional inactivation of pRB and p53 by the high-risk HPV E7 and E6 oncoproteins allow a cell to undergo and support DNA replication in an uncontrolled and unchecked manner. This averts eradication of cells with abnormal genomes and permits accumulation and perpetuation of genomic abnormalities (figure 4).

5.3. Abrogation of telomere erosion

Normal cells contain a built-in timer that ensures that they undergo only a finite number of cell divisions. With each round of genome replication the tips of the chromosomes shorten. Chromosomes are capped by repetitive DNA sequences (telomeres). Once they have eroded to a critical length, cells irrevocably withdraw from the proliferative pool and undergo replicative senescence (reviewed in 67). To overcome this limitation the high-risk HPV E6 protein increases expression and activity of telomerase (68), a ribonucleoprotein with reverse transcriptase activity that normally retains telomere length in stem cells.

In summary, through subversion of a small number of critical cellular pathways high-risk HPV E6/E7 expressing cells aberrantly enter DNA synthesis, lack the normal surveillance function of p53, and have overcome the replicative restriction of telomere erosion.

The general importance of the regulatory pathways targeted by high-risk HPV E6 and E7 for human carcinogenesis is illustrated by the fact the majority of human cancers show activation of telomerase and inactivation of the p53 and pRB pathways.

6. HPV E6 AND E7 AND MALIGNANT PROGRESSION

Even though high-risk HPV oncoproteins can dysregulate important growth regulatory and tumor suppressor pathways, most infections with high-risk HPVs cause benign lesions that do not undergo malignant progression or do so long after the initial infection. Similarly, high-risk HPV E6/E7 expressing keratinocytes undergo immortalization and can form stratified structures that resemble premalignant lesions. Only after prolonged

culture or by introducing an additional oncogene, do these cells acquire a fully transformed phenotype (69-71).

These observations suggest that additional cellular abnormalities are accumulated that contribute to the fully transformed phenotype. Several cytogenetic changes have been detected that frequently occur in cervical tumors (reviewed in 72). Gain of the chromosome 3q material appears to occur frequently and in concert with the transition of a premalignant lesion to malignancy (73).

Due to compromised p53-controlled G1/S and mitotic checkpoint controls it is conceivable that high-risk HPV expressing premalignant cells are particularly inept to recognize DNA damage and hence are prone to accumulate and propagate genomic abnormalities. Consistent with this notion it was shown that high-risk E6/E7 expressing cells show increased genomic instability. While E6 expressing cells mostly showed gene amplifications, abnormalities consistent with p53 loss, E7 expressing cells often displayed gains and losses of entire chromosomes and were aneuploid (24).

Aneuploidy is the most frequent manifestation of genomic instability in tumors overall and is caused by mitotic abnormalities. Of particular interest for the genesis of cervical cancer is the fact that abnormal, tripolar mitoses have been described as diagnostic hallmarks of high-risk HPV positive lesions (74, 75). A bipolar arrangement of the mitotic spindle is paramount for accurate symmetrical chromosome segregation during mitosis. As a consequence the synthesis of the mitotic spindle pole bodies, the centrosomes is intimately linked to the cell division cycle (reviewed in 76). Expression of the high-risk HPV E7 protein rapidly uncouples centrosome duplication from the cell division cycle and induces abnormal synthesis of centrioles, the core components of centrosomes. This leads to increased centrosome numbers and abnormal, multipolar mitoses and aneuploidy (42, 77).

Hence in addition to containing compromised surveillance functions high-risk HPV E6/E7 expressing cells constantly produce mitotic abnormalities even when expressed from viral episomes (25). This greatly increases the probability of malignant progression.

7. CONCLUDING REMARKS

In recent years a great deal has been learned concerning the oncogenic mechanisms of cervical cancer associated high-risk HPVs. Much less is known about the transforming properties of other cancer-associated papillomaviruses, in particular those detected in EV and non-melanoma skin cancers. There is little evidence to date, that these viruses contribute to cellular transformation by interfering with similar cellular pathways as the mucosal high-risk HPVs.

In addition, one has to remember; that the oncogenic functions of high-risk HPV E6 and E7 reflect the replication strategy of this class of HPVs, and carcinogenic progression and HPV genome integration is a terminal

event and not a reflection of the normal life cycle. If anything the propensity of these viruses to undergo inactivation by integration, which has been linked to the ability of high-risk HPVs to induce genomic instability ought to be an evolutionary predicament.

Curiously, the E6 and E7 proteins of low-risk HPVs do not share many of the cellular targets and biological activities of the corresponding high-risk HPV proteins. Low-risk HPV E6 and E7 proteins do not appear to induce telomerase activity and do not target p53 and pRB for degradation. Moreover, they do not score as oncogenes in standard transformation assays. Regardless, the low-risk HPVs are evolutionarily successful, thriving viruses with a very similar tissue tropism and identical requirements to replicate their genomes and produce progeny virus in terminally differentiated squamous epithelial cells that are bare of replication enzymes. Why these two groups of similar HPVs have developed such different replication strategies to overcome similar obstacles remains a mystery. One might speculate that it may be related to differences in the specific host cells of these two groups of HPVs.

8. ACKNOWLEDGMENTS

The work in the authors' laboratory is supported by Public Health Service Grants R01 CA81135, R01 CA66980, and P01 DE00275 to Karl Münger. The much-valued unceasing support by J. Daniels and S. Kcubrats is gratefully appreciated.

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Key words: Viral oncogenesis, Cervical Cancer, E6, E7, oncogene, p53, Retinoblastoma, Tumor Suppressor, Review

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