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Mechanism of action of human papilloma virus in cancer

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Abstract
Human papillomaviruses (HPVs) are associated with human cancer. HPVs cause various epithelial lesions due to their infection. Cell differentiation process of infected host cell is closely related to the viral life cycle of HPV. Immune system plays a vital role to control HPV infections. HPVs genomes encode eight translation open reading frames (ORFs) depending on splicing and sites of transcriptional initiation. HPV 16, a high risk human pappiloma virus (HR-HPVs), is associated with the vast majority of HPV positive HNSCC. HPV 16 E7 acts as the dominant viral oncogene in cervical, anal and head & neck carcinogenesis. Pocket Protein Supress Head and neck Cancer. p21Cip1 functions as a tumor suppressor in cervical carcinogenesis and inactivation of p21Cip1 by HPV-16 E7 partially account for the contribution of HPV-16 E7 to cervical carcinogenesis.

Keywords: Cancer, HPVs., cervical carcinogenesis, epithelial lesion

Introduction

Human papillomaviruses (HPVs) are small non- enveloped viruses containing double stranded circular DNA genomes. Recently, 200 HPV genotypes (approximately) are identified [1]. Initially 200 genotypes are distinguished by differences in the nucleotide sequence in a portion of L1 gene that encode the major capsid protein [2]. HPVs (epitheliotropic viruses) cause a number of different kinds of epithelial lesions due to their infection. If HPVs primarily infect skin or mucosal epithelia lining of the anogenital tract and head/ neck region (e.g. oral cavity, larynx) then they are classified as 'cutaneous' according to their tissue tropism. Mucosotropic HPV types can be further subdivided into 'low risk' and ' high risk' HPVs on the basis of their association with human cancer. HPV6 and 11 (Low risk HPV) cause genital warts and condyloma, but they are rarely associated with malignant lesions [3]. HPV16 (high risk HPV) are most commonly associated with cancers.

Researchers begin to postulate and analyse a possible role of HPV in cervical cancer in between 1974-1976.Two reports outlined the appearance of koilocytes (a papillomavirus particle-producing cell) in cervical smears indicates the presence of a papillomavirus infection (Meisels and Fortin, 1976). It might be possible to differentiate between benign, warty lesions that do not cause cervical cancer and non-viral precursor lesions that cause cervical cancer [3]. The expression of specific viral genes such asE6 and E7 was shown in cervical cancer cell lines and cancer biopsies, for integrated genome copies a specific opening within the viral ring molecule was shown and immortalization property of viral DNA and the encoded viral oncogenes supported the initial suspicions [48].

Cell differentiation process of host cell it infects is closely related to the viral life cycle of HPV because HPVs genomes are too small to encode many genes. The viral life cycle such as replication and transcription of the HPV genomes largely depend on host machinery. The first step in the viral life cycle might involves infection of cells within the basal compartment of stratified epithelia. The proliferating component of stratified epithelia are called basal cell. For the establishment of the viral genome as a nuclear plasmid in the infected cell, progression of basal cell through mitosis are found to be critical. After the entry of virus, HPV genomes become established as low copy number nuclear plasmids and then are stably maintained within the basal cells during cell proliferation / division [4]. Due to basal cell division some daughter cells get detached from the basement membrane normally bound by basal cells. This detachment commences the terminal differentiation of the host cell. The productive stage of the viral life cycle is triggered by the differentiation of HPV-positive epithelial cells. In the productive stage, the viral genome is amplified, late genes encoding structural and other proteins are expressed and progeny virus is made. Cellular DNA synthesis machinery, which is normally shut off in differentiating epithelial cell, is required for the amplification of the viral genome again. Reactivation of the host cellular replication machinery is done by disrupting normal differentiation programme of host cell with the help of early gene products of HPVs and drive the cell back into the cell cycle. Coincidentally, along with the amplification of the genome, late gene products are expressed, newly synthesized viral genomes are encapsidated and progeny virus particles are then released from the uppermost layer of the epithelium into the environment where they can infect another host.

Host control of HPV infection

Immune system plays a vital role to control HV infections. Due to prolonged persistence of squamous intraepithelial lesions in immunosuppressed women and increased incidence of HPV infections, it can be indirectly deduced the immune system is important in the control of HPV infection. During the course of regression the involvement of T helper cell in regressing lesions and a concomitant detectable humoral and cellular immune response against HPV antigens are evident. The escape of high–grade SIL and carcinomata in situ from immunological control seems to be based on different modifications of the cellular

antigen-presenting system, which might involve the proteasome transportation system, the HLA receptors and the cellular recognition system for presented oligopeptides. The escape from immune- surveillance mechanisms emergesas one important step in the progression of HPV-linked tumors [48].

Viral proteins of Human Papillomavirus:

Generally, HPVs genomes encode eight translation open reading frames (ORFs) depending on splicing and sites of transcriptional initiation. The ORFs encode one or more viral proteins. Viral proteins are designated as E and L protein. E means early protein, L means late protein. These designations are done on the basis of their pattern of expression in the viral life cycle. Late proteins are expressed only in the terminally differentiated epithelial cellsin the upper layers of a stratified epithelium. The early proteins are expressed throughout the life cycle i.e., beginning early after the initial infection of basal cells. The viral late proteins such as L1 (major capsid protein) can self assemble into virus like particles. These particles are used for the generation of recently available VLP based HPV vaccines and L2 (minor capsid protein) is assumed to facilitate encapsidation of viral DNA and viral infectivity [5]. Early proteins such as E1 and E2 are required for viral genome replication and maintenance. Replication of the viral DNA is done by E1 because E1 has both adenosine triphosphatase (ATPase) activity and associated with DNA helicase activity. E2 has high affinity for DNA sequence elements on the viral genome. Facilitation of the inheritance of the viral genomes to daughter cells during cell division is done by E2. The function of E4 is not yet known. It is argued to play a role in facilitating amplification of the viral genome and regress of progeny virus from terminally differentiated cells.

High risk HPV types include E5, E6 and E7 confer transforming properties to cell in tissue culture and tumorigenic properties in the context of laboratory animal based studies apart from contributing to the viral life cycle. Morphological transformation in rodent and human keratinocytes occur probably by increasing the epidermal growth factor receptor (EGFR) activity which causes the stimulation of cellular DNA synthesis. This transformation is carried out by E5 gene of mucosotropic HPVs such as HPV-6 and HPV-16 [6]. Immortalization potential of HPV-16, E6 and E7 in primary humn keratinocytes are enhanced by HPV -16E5. Apart from this, HPV- 16E5 stimulate the proliferation of human and mouse primary cells in cooperation with E7. All HPV genotypes do not contain E5 ORF. From the studies of skin and cervical carcinogenesis in mice it is clear that HPV-16E5 acts as an oncogene [7, 8]. HPV-16E5 induce epithelial hyperplasia. Epithelia hyperplasia diminished in case of mice expressing a dominant negative form of EGFR [9]. In the context of the HPV-16 life cycle, E5 plays a quantitative role in augmenting the level of viral genome amplification within the differentiating compartment of the stratified squamous epithelia [9].

In the tissue culture, the transforming properties of HPV-16E6 anf E7 gene encode proteins are more stronger than HPV-16 E5. In human cancer E6 and E7 are normally found to be expressed. Indeed, in many HPV-associated cancers, integration of the viral genome into the host genome leads to the selective retention of intact E6 and E7 genes, which continue to be expressed. Cells retaining the HPV-16 genome as a nuclear plasmid provide less powerful growth advantage over HPV-16 integration events and this correlates with increased expression of E6 and E7 owing at least in part to increased mRNa stability. E2 transcriptional regulator inhibit transcription of the E6 and E7 genes. Apoptosis or the senescence of the HPV-positive cervical cancer derived cell lines occur due to the loss of expression of E6 nd E7 [10]. HPV-16 E6 and E7 cooperate to induce immortalization of human oral, cervical and foreskin keratinicytes, mammary epithelial cells, bladder epithelial cells and a number of other epithelial as well as non –epithelial cell types [11]. In order to transform a variety of cell types E6 and E7 can also cooperate with other known oncogenes. In mice, tomors in many tissues express high risk HPV E6 and E7 genes. The role of E6 and E7 in oncogenesis are supported by a number of data.HPV-16 E6 and E7 of other high risk HPVs has the ability to bind to the tumor suppressor p53 in the ternary complex with E6 AP (ubiquitin ligase) causing proteosome –mediated degradation of p53. Functions of p53 in controlling cell growth and trigerring apoptosis in response to cell stress including DNA damage are inhibited by E6. Inactivation of p53 by E6 contributes to some of its transforming properties in tissue culture and its tumorigenic properties in mice [12, 13] E6's inactivation of p53 is also believed to play a critical role in the HPV-16 viral life cycle, as viral genomes carrying mutations that render E6 unable to ind to p53 fail to become established as nuclear plasmids. Other cellular proteins including PDZ proteins can bind with high risk HPV E6. Cellular proteins can interact with each other contributing to the E6's transforming activities in tissue culture and tumorigenic properties in vivo in context of mice [14-18].

High risk HPV E7 plays important function not only in the viral life cycle, but also in the malignancies arising from HPV-infected cells. Within the differentiating compartment of the stratified epithelia HPV E7 creates a cellular environment which allows the amplification of the viral genome in the viral life cycle. An E7 –deficient HPV-16 genome fails to induce DNA synthesis within the suprabasal compartment and fails to amplified its genome in the context of epithelial organotypic cultures of human foreskin keratinocyte cells. Moreover, a E7 –deficient HPV-16 genome expressed reduced levels of the capsid protein L1 [19].

In the context of oncogenesis, studies in mice have demonstrated E7 to be the dominant HPV-16 oncogene in the context of cervical [20], anal [21] and head /neck [22] carcinogenesis.

HPV- associated cancers

5 % of all cancers occur worldwide due to HPV infection. High risk HPV types causes several types of cancer such as cervical, vulvar, vaginal. Penile, anal and a subset of head and neck cancers [23-25]. Only in USA, every year more than s20, 000HPV associated cancer occurs in women. Amongst the cervical cancer is commonest (more than 12,000 cancer every year). Oropharyngeal cancer is also very much common (more than 11,000 men in USA).

Throughout the world second common cancer in women is cervical cancer.But the treatment has improved because both the incidents and mortality rate decreses over the past several decades in advanced coutries including United States [23, 26]. However, the incidents of cervical cancer has remain high in the devoloping countries which lack the resources for widespread screening programmes, such as Pap smear and more recently HPV DNA test. It can be thought partially that cervical

cancer devolops due to persistant infections with high risk HPVs. 50-60% (approx.) of cervical cancers occur due to HPV type16 (High risk HPV types). It's occurrence depends on the gepgraphical location. HPV 18 is also resposible for 14% of cervical cancer. The sixth leading cancer worldwide is Head and Neck sqamous cell carcinoma (HNSCC). It can arise in the oral cavity, oropharynx, larynx, and hypopharynx [27]. Uses of tobaco and consumtion of alcohol are the most important factors of HNSCCs. High risk type of HPVs are etiologically linked to approximately 20% of head and neck sqamous cell carcinomas. HPV 16, a high risk human pappiloma virus (HR-HPVs), is associated with the vast majority of HPV positive HNSCC [24, 25].

Oncogenic properties of high risk HPV E7

E5,E6 and E7 –these three oncogenes are encoded by HPV type 16. Among these viral oncogenes E7 seems to be the most potent oncogene in HPV-associated carcinogenesis. From the studies of tissue culture it is evident that high risk HPV E7 can able to induce immortalisation in primary human keratinocytes, co expressed with E6. Apart from this, dysregulation of various cellular processes such as gene transcription, aberrant DNA synthesis, protein degradation, epigenetic reprogramming, genomic integrity, and cellular metabolism [28] are done by high risk HPV E7. HPV 16 E7 acts as the dominant viral oncogene in cervical, anal and head & neck carcinogenesis. It is evident from the research work of HPV associated human cancers using transgenic mouse model [17, 20]. However, it remains largely unclear by what mechanism(s) E7 induces cancer. 100 cellular proteins are associated wuth HPV 16 E7 [29]. Thus, it is responsible to predict that E7 causes cancer thouigh multiple functions.

Relevant Targets of HPV16 E7 in HPV associated carcinogenesis

Among 100 cellular proteins that are associated with HPV 16 E7, the retinoblastoma protein is the best characterise. The retinoblastoma tumour suppressor protein (pRb) is a member of a family of three closely related proteins that includes p107 and p130, which have a highly conserved sequence in their so called pocket domain. pRb, a critical cell cycle regulator, regulates the transition of cells from G1 to S by binding partly and modulating activity of members of the E2F family of transcription factors [30]. Under normal condition, pRb supressor cellular proliferation [35], stimulates differenciation senescence [31, 32], cell survival [33], and maintanance of stem cell quiscence [34]. In addition, pRb functions as a tumour supressor in various types of tissues [35]. When bound by the high risk HPV E7 oncoproteins, pRb is dissociated from E2F transcription factors and degraded through a protiosom dependend degradation pathway. In activation of pRb is not sufficient to account for E7's oncogenic potential in context of cervical as well as head/neck carcinogenesis [22, 36-38].

The two proteins of a pocket protein family can be bound to and degraded by E7. Small DNA tumor viruses with high transforming potential such as Adenovirus EA and SV 40 large T antigen encode both p107 and P130 originally which rare identify as targets of viral oncoprotein. All 3 pockets proteins share some importants biochemical function. Sequence in the large C-terminal domain of pRb are homologous with small p107 and small p130 at a high degree. Association of the members of the E2F familily of transcription factors and all 3 pocket proteins play an important role. Cyclin/ Cdk complexes regulate the biochemical activities of all 3 pocket proteins through phosphorylation. There are several distinct differences among pocket protiens. pRb primarilly binds to transcriptions activator members of the E2F family, E2F 1-3, p107 and p130 primarilly binds to transcription repressor members of the E2F family, E2F4 and 5.

In various types of human cancers it has ben reported that the cancer cause due to genetic or epigenetic alteration of RB. [35]. Such changes in p107 and p 130 are rarely observed. It is clearly evident from an experiment with mice that E 107 and / or p 130 can acts as tumour supressor in the context of some tissues [39-42]. HPV-16 E 7 can bind to an inactivate p21CIP1 [73, 74]. p21CIP1 is a cyclin dependent kinase inhibitor which is a potentially relevant target of HPV-16 E 7 that plays an important role to regulates cell cycle.

Pocket Protein Supress Head and neck Cancer

HR-HPVs such as HPV 16 encode for 3 oncogenes (E 5, E 6 and E 7) (45). HPV + HNSCC express E6 and E7 much like in cervical cancer (46). HR-HPV E6 binds to an induces to the degradation of p53, while HR-HPV E7 binds to an induces to the degradation of pRb and its relatate pocket protein family members, p107 and p130 [3, 45]. From a study where HPV 16 transgenic mice were treated with the chemical carcinogen 4-nitroquinoline1-oxide (4NQO) it is reported that HPV-16 E 7 is the dominant viral oncogene in HPV associated HNSCC [22, 46]. From a study it has been found that combiantional loss of pRb along with either p107 or p130 with pRb in the epithelia causes head and neck cancer in mice. Severity of disease can't be differentiated that seen in E 7 transgenic mice. The oncogenic phenotype in mice deficient for both p107 and pRb was more severe than in mice deficient for both p130 and pRb. The hypothesis is that primarily E 7 oncogenic properties in HPV + HNSCC are driven by E 7 in activation of the two pocket proteins. The higj degree susceptibility of p107/pRb deficient mice to head and neck cancer is consistent with the hypothesis.

HPVE7 oncoprotein overrides p21Cip1's tumor suppressor activity in cervical carcinogenesis

E7 can dysregulate the cell cycle through its interaction with several cellular proteins including the retinoblastoma suppressor protein, pRb as well as the cdk inhibitor, p21 Cip1. Inactivation of pRb in cervical epithelia is not the only reason to explain the ability of E7 to cause cervical cancer. Presently, role of p21Cip1 in cervical cancer is focussed. Ability of E7 to induce cervical cancers was not significantly enhanced on the p21 null background consistent with the hypothesis that E7's ability to inhibit p21Cip1 contributes to its carcinogenic properties. Moreover, cervical carcinogenesis in mice expressing a mutant form of HPV-16 E7, E7CVQ,that fails to inactivate p21Cip1,was significantly reduced compared to that in K14E7WT mice expressing wild type HPV-16 E7.It has not only the capacity to inactivate p21Cip1 but also contribute to cervical carcinogenesis. It can be concluded that p21Cip1 functions as a tumor suppressor in cervical carcinogenesis and inactivation of p21Cip1 by HPV-16 E7 partially account for the contribution of HPV-16 E7 to cervical carcinogenesis [47].

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