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Review Article

Carcinogenic mechanisms of oncoproteins in high-risk human papillomavirus

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Abstract: Human papillomavirus (HPV) has more than 170 types, including 15 to 18 high-risk types that cause cancer. HPVs infect keratinocytes of the epithelium only. The DNA of high-risk HPVs integrates into cellular genome and then over expresses two kinds of oncoproteins, E6 and E7. The E6 and E7 oncoproteins inhibit tumor suppressor genes p53 and pRb respectively, resulting in the deregulation of cell cycle control, the inhibition of apoptosis, and the activation of telomerase activity that leads to cellular immortalization. Eventually the infected cells are transformed and malignant tumors occur.

Keywords: Human papillomavirus, oncoprotein, tumor suppressor protein, cell cycle, apoptosis, telomerase

Introduction

Human papillomavirus (HPV) is a kind of papilloma virus that infects human beings. More than 170 types of HPVs have been discovered so far, of which 15 are high-risk types that can cause cancers and 3 are possibly high-risk types [1, 2]. Most known types of HPVs are low-risk HPVs that do not cause any disease or cause benign hyperplasia of the skin only [3]. High-risk HPVs are typically transmitted through sexual contacts and can cause cancers at genital or other parts of the body. The oncogenic mechanisms of high-risk HPVs are primarily mediated by E6 and E7 oncoproteins, which interfere with cell cycle, inhibit apoptosis, and activate telomerase that results in cellular immortalization, eventually leading to malignant transformation of the infected cells and the development of cancers. Here, we reviewed the research progresses on high-risk HPVs and the oncogenic mechanisms of their oncoproteins.

The life cycle of HPV and its relationship with tumor

The life cycle of HPV

HPV is a non-enveloped virus with a particle diameter of 50-55 nm. The shell of the virus is of icosahedral symmetry, including 72 shell particles. The concentration of intact viral particles in suspension of cesium chloride is 1.34 g/mL. HPV genome is composed of closed circular double-stranded DNA, with a molecular weight of 5×10^6 Dalton and 7900 base pairs. According to functions, HPV genome can be divided into early region (E region), late region (L region) and non-encoding long control region (LCR). E region contains E1, E2, E4, E5, E6 and E7 open reading frames (ORFs), which encode proteins associated with viral replication, transcription, regulation and cell transformation. L region contains L1 and L2 ORFs, which encode major capsid protein and minor capsid protein, respectively. LCR is located between E and L regions, responsible for the regulation of transcription and replication [4]. Like other papilloma viruses, HPV only proliferates in keratinocytes in skin and mucosa, and its replication cycle strictly follows the differentiation program of host epithelial cells [5]. HPV virus enters epithelial tissue through minor skin lesions such as sexual intercourse and skin abrasion. The virus binds available receptors on cell surface such as α-integrin or laminin, and enters epithelial cells of basal layer via endocytosis mediated by clathrin and/or caveolin. Then, viral genome enters the nucleus by an unknown mechanism, replicates 10-200 copies, and generates prog-

eny virus products by transcription and translation as the division and differentiation of basal layer cells. The infection process of the virus from adsorption on the cells to the transcription of viral genome takes about 12-24 hours [5]. HPV infection does not cause cell lysis. The virus particles are released from the cells by degenerative changes of the cells. *In vitro* culture of HPV on cells has not yet been successful. HPV is especially easy to survive and proliferate in a warm, humid environment. Therefore, the external genital organs of male and female are the most easily infected sites. In HPV-infected tissues, viral DNA can be integrated into the cell genome, and the integration of viral genome promotes cell proliferation and increases the possibility for malignant transformation [6].

The relationship between high-risk HPVs and cervical carcinoma and other tumors

The known 15 high-risk HPV types include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82. The 3 probably high-risk types are types 26, 53 and 66. Among these, type 16 has the strongest carcinogenicity, and type 18 has the second strongest carcinogenicity [2]. The above types can cause canceration of the cervix by sexual transmission, or cause cancers at vagina, vulva, penis, and anus [7, 8]. However, not all infections cause canceration. In most cases, the virus can be eventually removed by the body without causing diseases [3].

Cervical cancer is a malignant tumor originated from epithelial cells of the cervix uteri. It is the fourth most commonly diagnosed cancer among females worldwide. In less developed countries, it is the second most common cancer and the third leading cause of cancer death in women [9]. It is shown that more than 90% cervical cancer cases are caused by HPV [10], and high-risk HPV DNA has been detected in 99.7% cervical cancer tissues [11]. Among all highrisk HPV types, types 16 and 18 cause 50% and 20% of all cervical cancer cases, respectively [12], and types 31 and 45 cause a total of 10% cervical cancer cases [13]. In 2012, around 528,000 cases of cervical cancer patients were diagnosed all over the world, leading to about 266,000 cases of deaths. In 2015, about 12,900 patients were diagnosed with cervical cancer in USA, leading to 4100 deaths [14].

It has been reported that 5.2% of all new cases of cancer in the world each year are caused by HPV infection [6]. Almost all cervical cancer cases, 85% anal cancer cases, and nearly 50% vaginal, vulva and penile cancers are caused by HPV infection [15]. In addition, HPV infection also causes oropharyngeal cancers, such as pharynx, soft palate, tongue and tonsil cancers. In USA, more than half of all oropharyngeal cancers are associated with infection by HPV type 16 [16]. The incidence of oropharyngeal cancers related with HPV infection has been increasing in the last 20 years, especially in men. It is estimated that the number of patients with oropharyngeal cancers caused by HPV in USA will exceed the number of patients with cervical cancer induced by HPV by 2020 [17].

Most of HPV infections are transient and the body's immune system can quickly remove the virus, so as to avoid the development of infection into canceration. In women, about 50% of the infection disappears within 8 months, about 75% of the infection disappears within 12 months, and about 97% of the infection disappears within 18 months [18, 19]. In 5-10% women, HPV infection can become persistent, and the persistent infection is likely to lead to precancerous lesions and the development of invasive cancer. From infection to canceration, it usually takes 10-15 years [20-22], or even 30 years [23]. The long latency period provides the possibility for the prophylactic treatment of cancer caused by HPVs.

Carcinogenic mechanisms of E6 and E7 oncoproteins in high-risk HPVs

HPV only infects stratified squamous epithelial cells (including skin and mucosa of genital tract, pharynx and anus), and does not enter blood circulation. In epithelial cells, HPV produces a number of proteins, including E6 and E7 oncoproteins produced by high-risk HPV, which are the only two HPV oncoproteins known by now. Overexpression of E6 and E7 oncoproteins generally requires viral DNA integration into the cell genome. The integrated viral genome is not complete, and cannot produce progeny viruses by replication. However, production of excessive E6 and E7 oncoproteins promotes the occurrence of cancers. Sustained overexpression of E6 and E7 oncoproteins in epithelial cells interrupts cell cycle, inhibits apoptosis, and activates telomerase, leading to

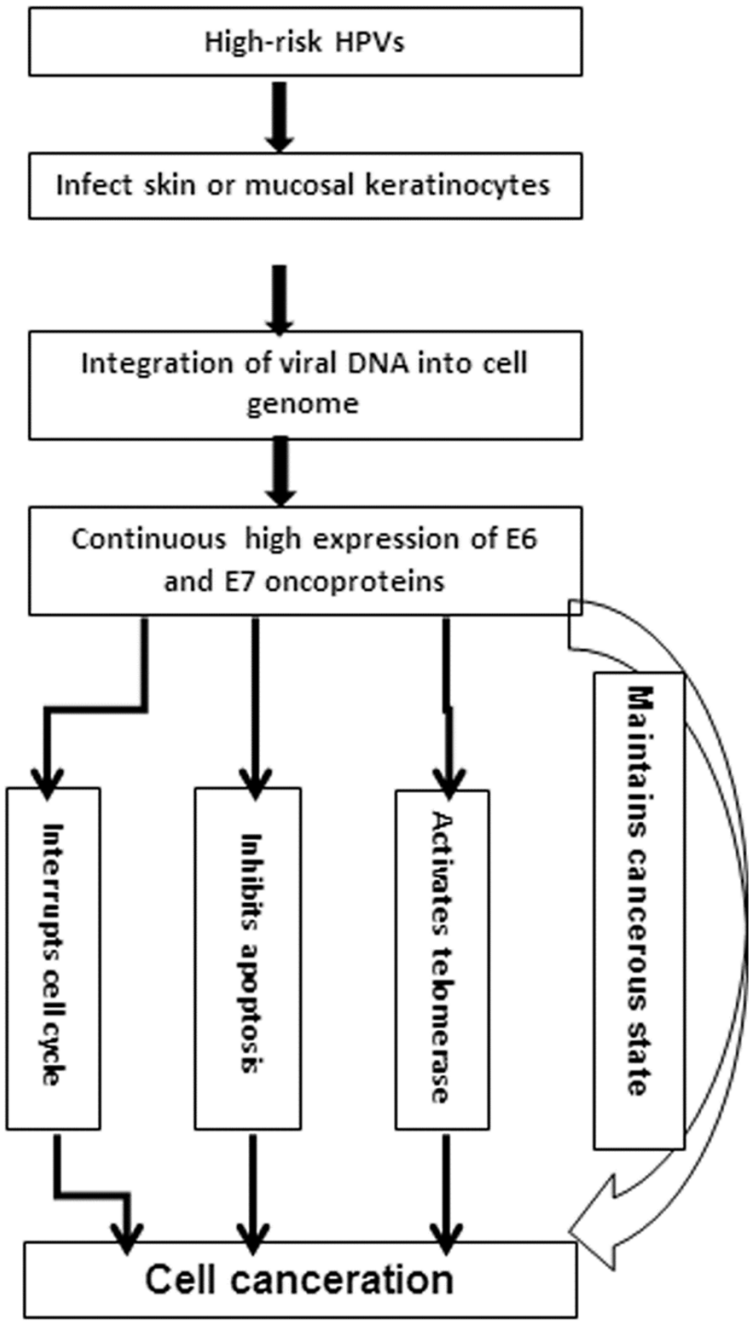

Figure 1. Schematic diagram of human papillomavirus carcinogenesis.

the immortalization of cells and finally canceration [24]. Continuous expression of E6 and E7 oncoproteins in epithelial cells causes cell carcinogenesis, and is required for the maintenance of the cancerous state (**Figure 1**).

Expression of E6 and E7 oncoproteins in host cells

After entering the nucleus of host cells, HPV gene is transcribed into polycistronic mRNA, which contains 8 overlapped ORFs that can be translated into 6 early proteins (E1, E2, E4, E5, E6 and E7) and 2 late proteins (L1 and L2). E1 and E2 proteins are first produced to regulate the replication of viral genome. E2 protein also regulates the transcription of E6 and E7 genes [25].

Viral genome can be replicated separately and eventually produce progeny virus. It can also be integrated into host cell genome. After the integration of viral genome into the genome of cells, progeny viruses are usually not produced because the genome is not complete. In particular, due to E2 protein expression disorders, it cannot inhibit the transcription of E6 and E7 genes to produce excessive E6 and E7 proteins, resulting in continuous high expression of E6 and E7 oncoproteins in infected cells [26].

E6 protein leads to excessive degradation of p53 protein

E6 protein contains 160 amino acid residues, and its main oncogenic mechanism is to promote the degradation of p53, a product of tumor suppressor gene, in proteasome. The content of p53 in normal cells is not high, but is increased rapidly when DNA in the cells is damaged. In addition, p53 can arrest cell cycle at G1/S, and maintain the integrity of cell genome by enhancing the expression of DNA repair protein. If DNA is severely damaged, p53 induces apoptosis, thereby avoiding the transfer of damaged genes to the next generation of cells. Continuous production and degradation of p53 in normal cells maintain its content at a certain level. Under normal circumstances, p53 is degraded by ubiquitin-proteasome system, in which murine double minute 2 (mdm2) protein acts as the ligase. In high-risk HPV-

infected cells, E6 protein is excessively expressed, and binds with E6-associated protein (E6AP). Therefore, the recognition characteristic of E6AP is changed and E6AP binds with p53 protein, leading to excessive degradation of p53 protein in ubiquitin-proteasome system. One consequence of excessive degradation of p53 protein is that the cells can not normally repair DNA damages. As a result, cell genome cannot maintain its integrity, and gene mutation accumulates, finally leading to malignant transformation of the cells [26-28] (**Figure 2**).

E6 protein inhibits apoptosis

The proliferation and apoptosis of normal cells are in a state of equilibrium. If this balance is destroyed, tumor may occur. E6 protein in high-risk HPV can inhibit cell apoptosis through several mechanisms. On one hand, p53 causes apoptosis of cells with permanently damaged DNA, in order to avoid the transfer of damaged or incomplete genome to progeny cells. it also regulates apoptosis through a variety of ways, while excessive degradation of p53 induced by E6 protein disrupts normal cell apoptosis [26]. On the other hand, E6 protein acts on the regulatory pathways of apoptosis. In normal cells, apoptosis-inhibiting proteins (such as Bcl-2) and apoptosis-promoting proteins (such as Bax) regulate cell apoptosis. In high-risk HPV-infected cells, overexpression of E6 protein up-regulates the expression of Bcl-2 protein and down-regulates the expression of Bax protein, leading to the inhibition of apoptosis [29, 30] (**Figure 2**).

E6 protein activates telomerase to make cells immortal

In somatic cells, every time DNA replicates, the new DNA chain is always dozens of nucleotides shorter than the template chain at 5' end because the RNA primer bound to the 3' end of template chain can not be replaced by DNA chain. With the division of cells, telomeres will gradually be shortened, until the time when the cells can no longer split. Therefore, regular somatic cells have limited life. Germ cells and stem cells have a mechanism to prevent the shortening of terminal DNA, which is the extension of telomere DNA using telomerase. Telomerase can extend the 3' end of the DNA chain using the RNA chain it carries as the template. When the extended template strand is replicated, even the RNA primer at 3' end cannot be replaced, the nascent DNA chain is still not shorter than the original template chain. As a result, germ cells and stem cells can proliferate indefinitely. Telomerase is also expressed in somatic cells, but its expression is down-regulated or its activity is inhibited in normal conditions. Therefore, normal somatic cells cannot be split after a certain number of times. Telomerase expression in malignant tumor cells is up-regulated or its activity is increased, so these cells can proliferate indefinitely. E6 protein up-regulates the expression of human telomerase reverse transcriptase (hTERT), resulting in immortal cells that can proliferate indefinitely [31, 32]. E6 protein can induce hTERT expression by interfering with multiple transcription factors through a variety of mechanisms [33]. E6 protein inhibits Maz protein, which suppresses hTERT transcription by binding to hTERT promoter. E6 protein can promote the binding of hTERT promoter with Sp1, which facilitates the transcription of hTERT. E6 protein also induces the hypomethylation of DNA base pairs at CpG island of hTERT promoter, which up-regulates gene transcription [34] (**Figure 2**).

E7 protein disrupts cell cycle by inhibiting the activity of tumor suppressor protein pRb

E7 oncoprotein is composed of about 100 amino acid residues. E7 oncoprotein exerts its oncogenic effect by acting on pRb protein, a product of tumor suppressor gene. Binding of E7 protein with pRb protein inhibits the binding of pRb with transcription factor E2F, and activates E2F. E2F is a transcription factor that regulates cell cycle and DNA synthesis. The activation of E2F promotes the replication of the cell genome and facilitates the transition of cell cycle from G1 phase to S phase, and hence enhancing cell proliferation. In normal cells with DNA damages, pRb binds with E2F and inhibits its transcriptional activity. As a result, cell cycle is arrested in G1 phase, the cells have more time to repair damaged DNA, and transfer of possible gene mutations to progeny cells is prohibited. In cells infected by high-risk HPV, E7 oncoprotein inhibits the function of pRb, and cells with damaged DNA can still enter S phase from G1 phase. As a result, cells continue to proliferate and eventually become cancerous [35, 36]. In addition to bind-

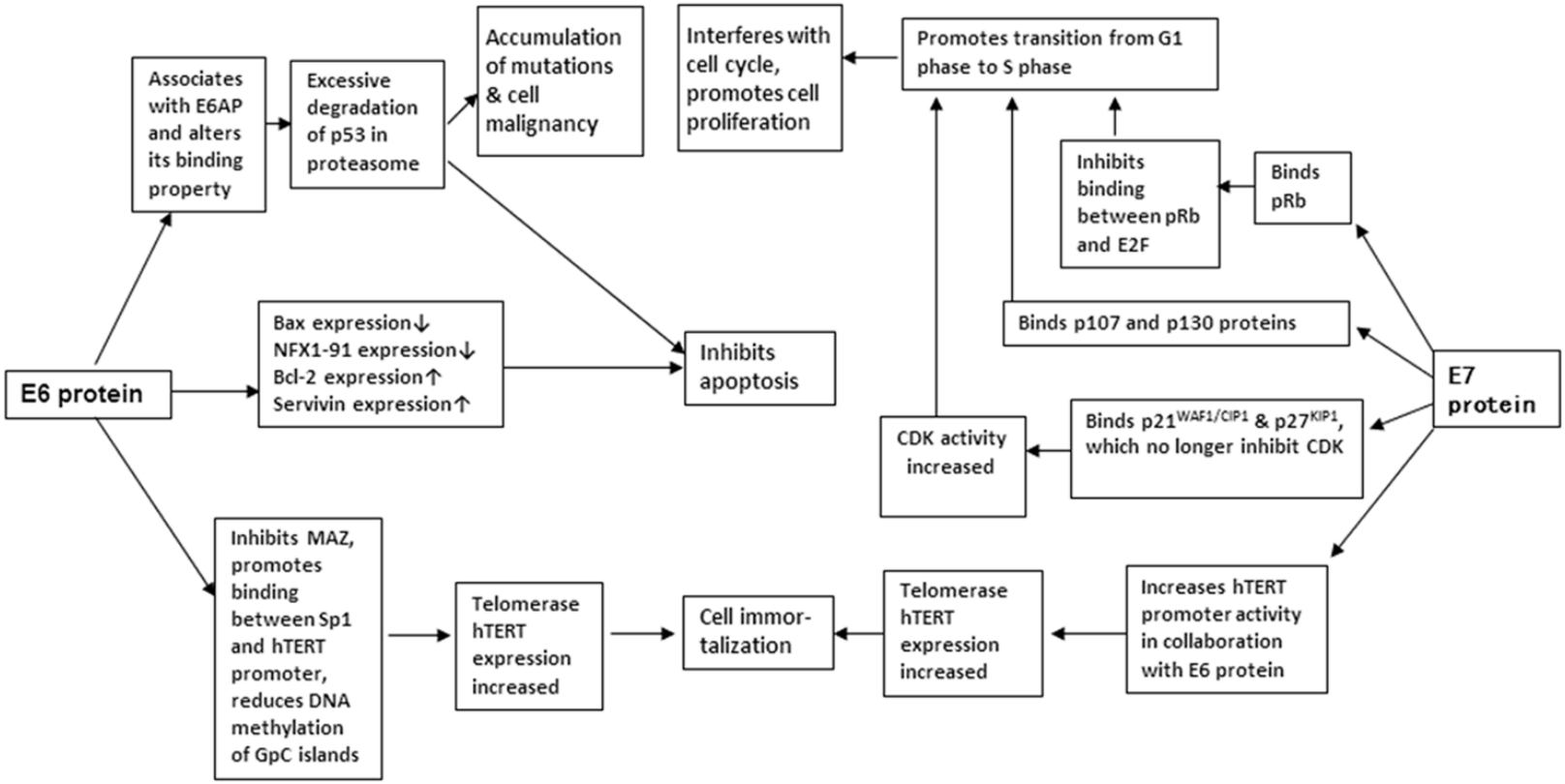

Figure 2. The mechanisms by which E6 and E7 oncoproteins interfere with cell cycle, inhibit apoptosis, and render the cells immortal. CDK, cyclin-dependent kinase; E6AP, E6-associated protein; hTERT, human telomerase reverse transcriptase.

ing with pRb protein, E7 protein can also bind p107 or p130 proteins, playing similar roles [37] (**Figure 2**).

Other mechanisms by which E7 protein induces carcinogenesis

In addition to binding with pRb, p107 and p130, E7 protein can disrupt cell cycle via other mechanisms. E7 protein can bind with cyclin-dependent kinase (CDK) inhibitors $p21^{WAF1/CIP1}$ and $p27^{KIP1}$, and abolish their inhibiting effect on CDK that is required to promote cell cycle. When E7 protein is co-expressed with $p21^{WAF1/CIP1}$ and $p27^{KIP1}$, the cells can enter S phase. When E7 protein is absent, the cells are arrested in G1 phase. E7 protein can also directly or indirectly act on the cell cycle protein A/CDK2 complex to disrupt cell cycle [38]. E7 protein can also improve the activity of hTERT promoter, promote the transcription of hTERT, and induce cell immortality by cooperating with E6 protein [39] (**Figure 2**).

E7 protein promotes cell dysplasia by stimulating the expression of human Pygopus 2 (hPygo2)

It is reported that the level of hPygo2 in highly proliferative lesions and squamous cell carcinoma is higher than that in normal epithelial cells in tumor progression microarrays of cervical carcinoma. In addition, mRNA and protein levels of hPygo2 in HPV-positive cervical cancer cells are higher than those in cells that are not infected by HPV. In cervical cancer cell lines, reduced expression of E7 protein that is induced by RNA interference promotes the binding of tumor suppressor protein pRb to hPygo2 promoter, while reduced expression of E74-like factor-1 (Elf-1) that is induced by RNA interference reduces the binding of pRb to hPygo2 promoter. Transfection of Rb with dominant activity inhibits the activation of hPygo2 that is dependent on Elf-1, whereas Elf-1 itself can increase the expression of hPygo2. Chromatin immunoprecipitation assay shows that Rb inhibits hPygo2 by suppressing Elf-1 at the Ets binding site of hPygo2 promoter. These results suggest that down-regulation of Rb caused by E7 protein can inhibit Elf-1 and stimulate the expression of hPygo2. Therefore, hPygo2 expression initiated by Elf-1 is needed by the proliferation of cervical cancer cells, and this expression can be used as an indicator of dysplasia [40-42].

Summary and comment

HPV causes cancer mainly through E6 and E7 oncoproteins. If the effects of E6 and E7 oncoproteins can be blocked, secondary prevention, preventive treatment or early treatment of malignant tumors caused by HPV can be achieved [43-45]. There are reports on the treatment or prevention of cancers induced by HPV through targeting E6 and E7 proteins or mRNAs. For example, the expression of E7 protein and the proliferation of cervical cancer cells can be inhibited using single-chain antibody variable region of E7 protein [46, 47]. Inhibition of E6 and E7 gene expression using small-interfering RNA induces the apoptosis of cervical cancer cells [48-51]. In addition, efforts have been made to block the effects of E6 and E7 oncoproteins by RNA aptamers prepared using systematic evolution of ligands by exponential enrichment (SELEX) technique [52, 53]. There are two large advantages for cancer prevention and treatment measures related with E6 and E7 oncoproteins. First, these measures target virus products, and do not cause damages to normal cells of the body. Second, the time from HPV infection to the occurrence of cancer (such as cervical cancer) is usually sufficiently long (10-15 years or even 30 years) making possible the secondary prevention or preventive treatment of cancers induced by HPVs [54, 55].

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Disclosure of conflict of interest

None.

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