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Review

The interaction of human papillomaviruses and adeno-associated viruses in suppressive co-infections

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ABSTRACT

Human papillomavirus (HPV) is one of the most common oncogenic viruses which cause malignancy in different epithelial surfaces of the human body and its infection is the main cause of cervical cancer. However, research suggests that this virus might not be the sole cause of infection in target cells. It is believed that, other infectious agents could co-infect the same cell with HPV including; bacteria, viruses, and parasites, which may have different effects on the carcinogenesis of HPV infections. One of the most important viruses is adeno-associated virus (AAV), which comes from the parvoviridae family. The function of this virus is associated with several stages of HPV carcinogenicity, which leads to the suppression of HPV oncogenesis. The inhibition effects of AAV are exerted not only in viral parts but also in cellular parts. This suppression illuminates a new therapeutic approach in the way of HPV-associated cervical cancer. In the present review we consider the exact roles of AAV infection in this suppression.

1. Introduction

Evolutionary, the relation of Human papillomavirus (HPV) infection and human's body have a far old history(Bravo and Félez-Sánchez, 2015). This virus is reported to be associated with several mucosal membrane malignancies including those of the cervix, anus, penis, oropharynx and vulva (Doorbar et al., 2012; Forman et al., 2012; Wakeham and Kavanagh, 2014). Among all of the cancer cases, 4.8% are associated with HPV infection and this infection is demonstrated to cause 8.6% and 0.8% of all cancer cases in women and men, respectively (Serrano et al., 2018). Furthermore, the effects of this viral infection could be correlated with some other clinical complications such as atherosclerosis (Hemmat et al., 2018). The International Agency for Research on Cancer (IARC) proclaimed 12 different types of high-risk (HR) HPVs to be carcinogenic for humans, including; types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (Bouvard et al., 2009). While, HPV-16 and HPV-18 are the most common types, which could be detected within neoplastic lesions (Smith et al., 2007), these viruses might not be alone when they infect their host cells.

Several studies demonstrate that some infectious agents could co-infect cells with HPV infection, including; *Schistosoma hematobium*, *Chlamydia trachomatis*, and several viruses including, *Human immunodeficiency virus (HIV)*, *BK virus (BKV)*, *Molluscum contagiosum*, and *Adeno-associated virus (AAV)* (Comar et al., 2011; Ferenczy et al., 2003; Freitas et al., 2009; Nonato et al., 2016; Payne et al., 1997; Petry et al., 2003). However, the roles of these pathogens in the development of HR HPV-associated cancers are functionally different.

AAV is a member of *dependovirus* genus which belongs in the *parvoviridae* family. The prevalence of various types of this virus varies from 38% to 72% in the general population (Boutin et al., 2010). This virus needs a supporter virion to pave the way for its replication. Without this supporter virion, the latent infection of AAV is accomplished (Wu et al., 2006). The ssDNA genome of AAV encodes four non-structural proteins (Rep78, Rep68, Rep52, and Rep40), and three structural proteins (VP1, VP2, and VP3) (Drouin and Agbandje-McKenna, 2013). It was shown that, the ongoing life cycle of AAV and synthesizing of its non-structural proteins, could inhibit and interact with carcinogenic processes of several other viral infections (e.g. HPV infection) (Hermonat, 1994). Furthermore, it has been determined that anti-AAV antibodies could be detected in patients with HPV-associated cervical cancer (Mayor et al., 1976). The prevalence of HPV/AAV co-infection was just found in one study, in which no significant relation was identified (Shafiei-Jandaghi et al., 2017). It has also been observed that the prevalence of this co-infection can be high in pregnant women,

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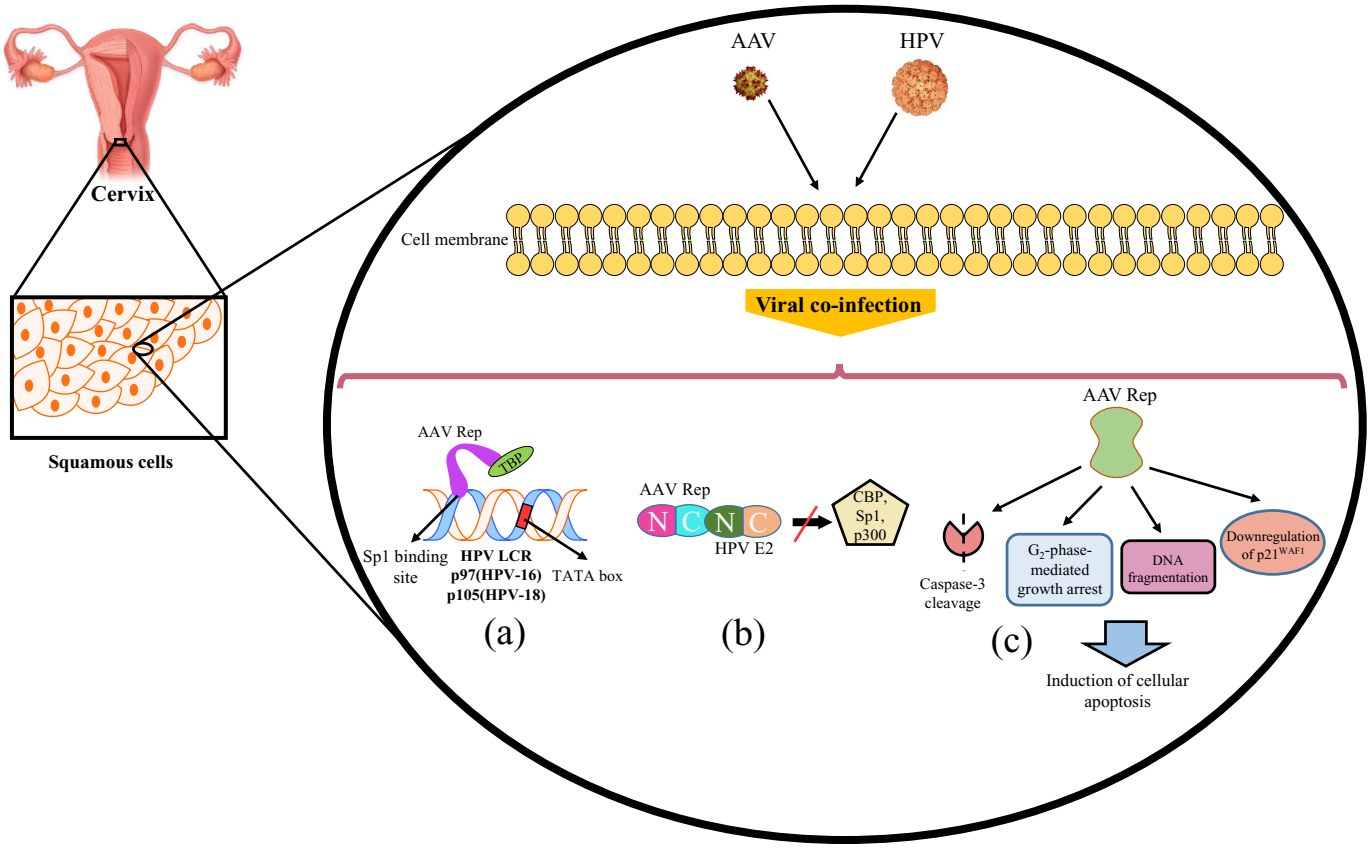

Fig. 1. Effect of HPV/AAV co-infection at molecular level on HPV carcinogenicity.
AAV Rep proteins bind to TBP and obstruct association of TBP and TATA box and also binds to Sp1 binding site which leads to inhibition of HPV LCR promoter activity (a). C-terminus of AAV Rep proteins disturb effectiveness of HPV E2 to recruitment of CBP, p300, and Sp1 by binding to N-terminus of E2 (b). AAV Rep protein activities give rise to caspase-3 cleavage, G_2-phase-mediated growth arrest, DNA fragmentation of host cell, and downregulation of $p21^{WAF1}$, by which cellular apoptosis get induced (c).

compared to non-pregnant women (Freitas et al., 2009). Despite the lack of reports about the exact co-infection time, it is believed that HPV/AAV co-infections could have an interaction before the integration phase of HPV infection, but also during the occurrence of cervical neoplasm; by attention of the targets of AAV protein in HPV life cycle, which are mentioned below.

In the following review, we consider the inhibition effects of AAV infection in the development of HR HPV-associated cervical cancer, and AAV proteins which are suspected to be involved in this procedure. Data for this review were identified by searches of PubMed, Scopus, Google, and references from relevant articles, using the search terms: Human papillomavirus and Adeno-associated virus, Human papillomavirus and coinfection.

2. Pathogenesis of HPV

The expression of HPV early proteins E1 (DNA helicase) and E2 (transcription factor and genome tether) lead to virus replication (Bedell et al., 1991; Stanley et al., 1989) Then, the existence of E5, E6, and E7 (as the viral oncoproteins) give rise to the proliferation of HPV-infected cells (Hemmat and Baghi, 2018; Kim et al., 2010; Park and Androphy, 2002; Thomas et al., 1999; Westphal et al., 2009). HPV proteins force differentiating suprabasal squamous cells to back into the cell cycle to reactivate cellular DNA replication and to increase the viral genome in number (Chow et al., 2010; Munger and Howley, 2002). Enhanced expression of regulatory transcription factors (activator proteins 1 and 2) could also occur as a result of HPV-induced carcinogenicity (de Wilde et al., 2008). An essential event during the process of HPV carcinogenesis is the deregulation of viral gene expression. Elevated levels of E6 and E7, in infected-cells, follow by pro-malignant effects in proliferated epithelial cells which leads to improved cell cycle entry and loss of differentiation in the epithelium (Pett and Coleman, 2007; Williams et al., 1998). Additionally, upregulation of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) could accelerate these events (Kohaar et al., 2007). Although the roles of Treg in pathogenesis of HPV are only recently demonstrated as a limitation for the effectiveness of immune activation against HPV infections, the exact mechanism needs to be further investigated (Ao and Zeng, 2018).

3. Interaction of HPV and AAV infections

3.1. AAV and long control region (LCR)

The transforming activity of HPV as described above is mediated by its three oncoproteins, E5, E6, and E7 by which, epidermal growth factor receptor (EGFR) degradation, p53 and pRB, (two of the essential tumor suppressors), are repressed. The expression of these oncoproteins is regulated by LCR, located upstream of the genes encoding E6 and E7 (Kim et al., 2010; Tommasino, 2014). Previous studies have found that AAVs might disrupt and inhibit the LCR promoter activities of HPV-18 and HPV-16 (Fig. 2) (Hermonat, 1994; Hörer et al., 1995). Although the exact mechanism involved in this inhibition was not determined, it has been identified that AAV Rep78 plays a key role in the incidence of this phenomenon. The target of Rep78 is located within the p97 core promoter of HPV-16 LCR and p105 core promoter of HPV-18 LCR, where a TATA box is recognized by TATA box-binding protein (TBP) and TBP is reported to be the target of Rep78(Fig. 1) (Su et al., 2000). TBP is one the important ingredients for the initiation complex of transcription by

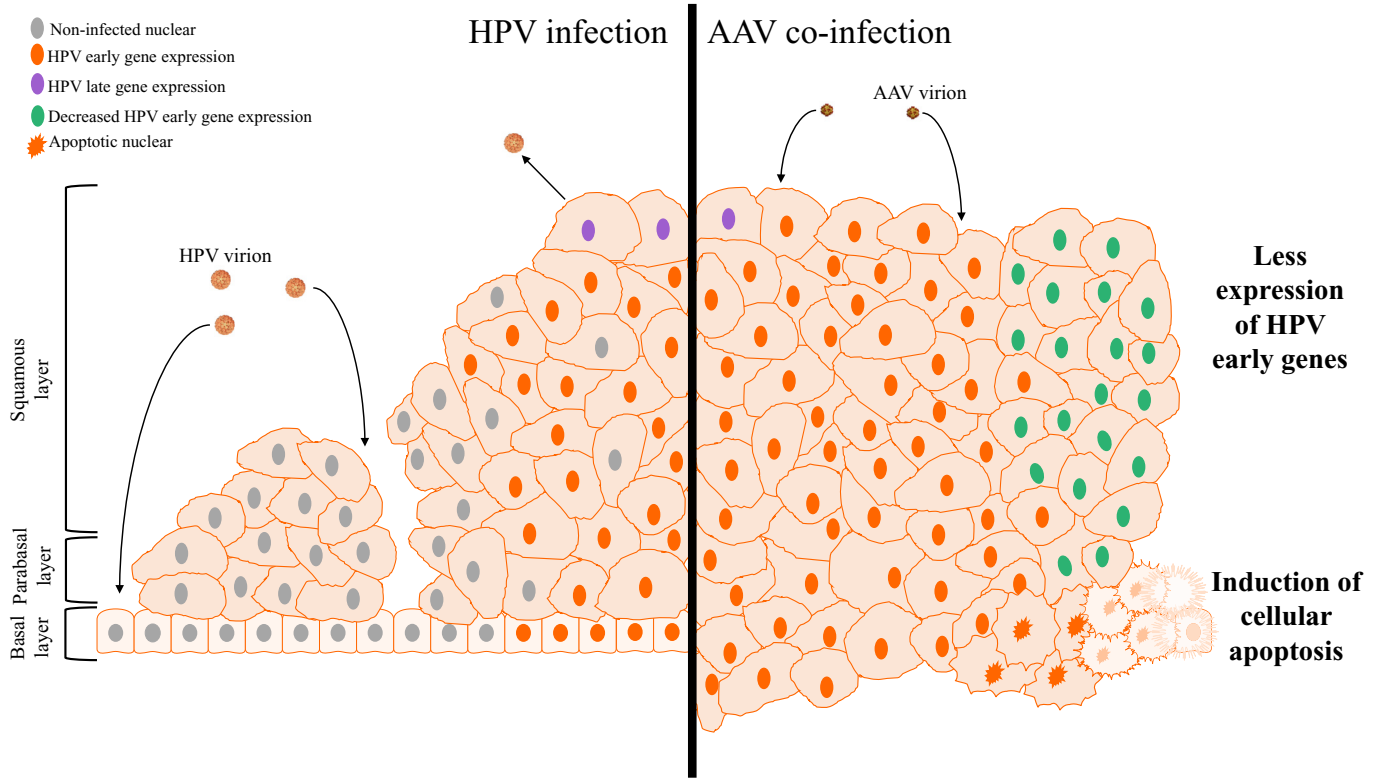

Fig. 2. Effect of HPV/AAV co-infection at morphological level.
HPV virions infect basal cells within basal layer or from a micro-trauma. The first step of infection is expression of HPV early genes such as E1, E2, E4, E5, E6, and E7. The infection continues to express HPV late gene and also carcinogenicity. AAV co-infection could inhibit the carcinogenic process of HPV by repressing its early gene expression which leads to two events, induction of cellular apoptosis and less expression of HPV early genes.

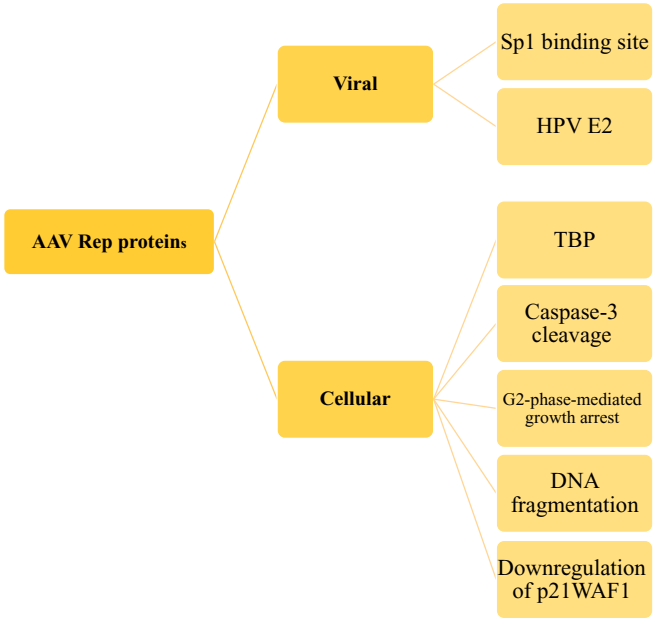

Fig. 3. Functions of AAV Rep proteins in viral and cellular parts.

RNA polymerases (Hochheimer and Tjian, 2003). Significantly, Rep78 could barricade TBP from binding to the TATA-box rather than disannulling the TBP-TATA complex. Additionally, the AAV Rep78 has been shown to interact with Sp1 (another transcription factor) and to suppress the function of the Sp1 binding site within the p97 promoter. However, the binding sites of TBP and Sp1 binding site are separated in the Rep78 molecule (Su et al., 2000).

3.2. Disruptive effect of AAV on HPV E2

HPV DNA requires two fundamental proteins, E1 and E2, in order to initiate its replication (Chiang et al., 1992). The roles of E2 in transcription and replication are exerted through its interaction with certain cellular proteins, including: Sp1, TBP, autocrine motility factor 1 (AMF-1), cAMP response element-binding (CREB) binding protein (CBP) and its related homologue p300 (Breiding et al., 1997; Lee et al., 2000; Li et al., 1991; Steger et al., 1995). All four types of AAV Rep proteins are divided into two major functional domains, C-terminal and N-terminal (Giri and Yaniv, 1988). It has been suggested that AAV Rep68 and Rep40 are associated with the inhibition of transcriptional activation of HPV E2-mediated promoters. The effects on E2 activities are related with C-terminal domains of Reps. This region, which is identical among all four Rep proteins, is correlated with the N-terminal transactivation domain of HPV E2. The inhibition effects of Reps on E2 do not disturb the binding of E2 to E1. Thus, they faze the interaction of other factors with the N-terminal of E2 such as CBP, or its homologue p300 (Fig. 1). AAV Rep proteins (Rep68 and Rep40) act as function disruptors of HPV E2 in the recruitment of p300 by E2 (Marcello et al., 2000).

3.3. $p21^{WAF1}$ CDK inhibitor with dual response to AAV infection

In non-permissive cells for AAV replication, AAV infection has been shown to decrease cellular proliferation and repress neoplastic cell growth by two factors, augmentation of pRb hypophosphorylation and upregulation of $p21^{WAF1}$ cyclin dependent kinase (CDK) inhibitor expression (Hermanns et al., 1997). HPV and its associated proteins are correlated with altered regulation patterns of the $p21^{WAF1}$ protein by AAV. However, in HPV-negative cells, AAV infection increases the $p21^{WAF1}$ expression rate which consequently leads to the suppression of cellular proliferation, and a reverse event occurs in HPV-positive cells.

Table 1
Questions which still need to be addressed concerning the effects of HPV/AAV co-infection in HPV life cycle.

No.	Unanswered questions
1	What is the rate of AAV infection in patients with regressed HPV lesions?
2	What is the rate of AAV infection in patients with progressed HPV lesions?
3	Is there any association between the level of immune response to HPV infection and HPV/AAV co-infection?
4	Do all types of AAV participate in disruption of HPV life cycle?
5	Is there any association between the rate of AAV infection and speed of HPV wound healing?

The decreased levels of $p21^{WAF1}$, upon infection with AAV in HPV-infected cells (Fig. 1), is associated with increased CDK2 kinase activity and upregulation of cyclin E protein expression (Sherr and Roberts, 1999), suggesting that, cyclinE/CDK2 complex activation follows a decrease in $p21^{WAF1}$. In order to activate CDK2 phosphatase activity should be triggered, which is mediated by AAV Rep proteins (Saudan et al., 2000). Normally, cyclin E protein and $p21^{WAF1}$ bind to each other with a certain tendency. In HPV-positive cells, HPV E7 binds to C-terminus of $p21^{WAF1}$ which is associated with differences in the interaction of cyclin E with $p21^{WAF1}$ (Alam et al., 2006; Funk and Galloway, 1998).

3.4. Apoptosis as a result of HPV/AAV co-infection

Some viral infections have been reported to have an association with cellular apoptosis (Ludwig et al., 2006; Yang et al., 2008). The expression of AAV Rep78 was demonstrated to be correlated with caspase-3 cleavage, which leads to apoptosis induction (Fig. 2) (Schmidt et al., 2000). Cervical cells, with the HPV genome, express high levels of Rep proteins when they get co-infected with AAV which aids apoptosis (Alam and Meyers, 2009). It is shown that HPV E2 proteins prepare a favorable environment for AAV replication and translation (Ogston et al., 2000). Furthermore, AAV infections are proven to be associated with G_2-phase-mediated growth arrest induction in cancerous cells with faulty p53 (Raj et al., 2001). DNA fragmentation as a stage of cellular apoptosis (Elmore, 2007), could be the consequence of HPV/AAV co-infection which is correlated with Rep78 activity (Berthet et al., 2005). Additionally, downregulation of $p21^{WAF1}$, which was mentioned before as the sequel of HPV/AAV co-infection, might prepare HPV-positive cells for subsequent events leading to apoptosis (Fig. 1) (Alam and Meyers, 2009).

4. Conclusion

Several infectious agents are reported to co-infect with HPV. These co-infections could have different effects on the carcinogenesis of HPV, whereby some intensify it and some suppress it. Among these co-infections, AAVs could have suppressive effects on HPV carcinogenesis. These effects could be exerted in viral parts or in cellular parts (Fig. 3). AAV Rep proteins play the key role in this event. AAV uses HPV to complete its transcription and replication, and HPV-infected cells use AAV to repress HPV activity. Regarding the fact that no diseases related to AAV have been reported in humans (Huser et al., 2017) but that there is a high prevalence of AAV infections in the human population (up to 80%) (Blacklow et al., 1968; Blacklow et al., 1971; Erles et al., 1999; Georg-Fries et al., 1984; Mayor et al., 1976; Sprecher-goldberger et al., 1971) indicates that, AAV infections could be introduced and used as a natural suppressors of HPV carcinogenicity. This is believed to be most efficient particularly in the early phase of HPV infections. Moreover, amplification of AAV Rep gene and transferring them to cancerous tissues, as a therapeutic method, should be considered in further studies.

Currently, HPV/AAV co-infections still remain a highly under researched topic of interest (Table 1). Thus, the suppressive function of AAV in HPV carcinogenicity process, and the role of individual AAV proteins, need to be further investigated.

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