Review

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APOBEC-mediated genomic alterations link immunity and viral infection during human papillomavirus-driven cervical carcinogenesis

Lanting Chen[1,2,3], Xuemin Qiu[1,2,3], Na Zhang[1,2,3], Yan Wang[1,2,3], Mingyan Wang[1,2,3], Dajin Li[1,2,3], Ling Wang[1,2,3,*], Yan Du[4,*]

[1] *Laboratory for Reproductive Immunology, Hospital & Institute of Obstetrics and Gynecology, IBS, Fudan University Shanghai Medical College, Shanghai, China;*
[2] *The Academy of Integrative Medicine of Fudan University, Shanghai, China;*
[3] *Shanghai Key Laboratory of Female Reproductive Endocrine-related Diseases, Shanghai, China;*
[4] *Office of Clinical Epidemiology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China.*

Summary **Cervical cancer is one of the most frequently diagnosed cancers and is a major cause of death from gynecologic cancers worldwide; the cancer burden from cervical cancer is especially heavy in less developed countries. Most cases of cervical cancer are caused by persistent infection with carcinogenic human papillomavirus (HPV) genotypes 16 and 18. Non-resolving inflammation caused by HPV infection provides a microenvironment that facilitates cancer development. Molecular alterations during the process of HPV-induced carcinogenesis are characterized by DNA methylation within the HPV genome, promoter hypermethylation of tumor suppressor genes in the host genome, as well as genomic instability caused by viral DNA integrating into the host genome. Catalytic polypeptide-like apolipoprotein B mRNA editing enzymes (APOBECs) normally function as part of the innate immune system. APOBEC expression is stimulated upon viral infection and plays an important role in HPV-induced cervical cancer. APOBECs catalyze the deamination of cytosine bases in nucleic acids, which leads to a conversion of target cytosine (C) to uracil (U) and consequently a change in the single-stranded DNA/RNA sequence. APOBEC proteins mediate the complex interactions between HPV and the host genome and link immunity and viral infection during HPV-driven carcinogenesis. Understanding the effects of APOBECs in HPV-induced cervical carcinogenesis will enable the development of better tools for HPV infection control and personalized prevention and treatment strategies.**

Keywords: Cervical cancer, human papillomavirus, inflammation, APOBEC

1. Introduction

Cervical cancer is the fourth most common cancer among women worldwide (*1*). There were about 527,600 new cases of and 265,700 deaths due to cervical cancer in 2012 (*1*). About 85% of the cases and 87% of the deaths occurred in resource-poor countries, posing a significant public health burden in these regions (*1,2*). In China alone, there were an estimated 98,900 new cases of and 30,500 deaths attributed to cervical cancer in 2015, and these figures were higher than those for any other type of gynecologic tumor (*2*). Moreover, the incidence of cervical cancer among young Chinese women (≤ 30 years old) has been increasing by 2-3% each year (*2*). Approximately 80% of cases of cervical cancer involve squamous cell carcinoma, which develops through pre-malignant lesions known as cervical intraepithelial neoplasia (CIN) that range from grade I to III (*3*). Cervical adenocarcinomas accounts

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*Address correspondence to:
Dr. Yan Du, Office of Clinical Epidemiology, Obstetrics and Gynecology Hospital of Fudan University, No. 419 Fangxie Road, Shanghai 200011, China.
E-mail: sophiedu_61@163.com

Dr. Ling Wang, Hospital and Institute of Obstetrics and Gynecology, IBS, Fudan University, 413 Zhaozhou Road, Shanghai 200011, China.
E-mail: Dr.wangling@fudan.edu.cn

for 10-20% of cases, with less well-characterized preceding stages. Almost all cases of cervical cancer are caused by persistent infection with certain carcinogenic human papillomavirus (HPV) genotypes (*4*). HPVs are a large and diverse group of viruses, with new types continually being identified (*5,6*). There are at least 15 genotypes of carcinogenic HPV, and the two most prevalent and carcinogenic types are HPV types 16 and 18 (*7*). The half-life of an infection with a high-risk HPV type is estimated to be 8-10 months. Infection with HPV-16 has the longest duration, with an average persistence of 16 months (*8*). HPV-16 causes more than half of all cervical cancers, while HPV-18 is implicated in many cases of endocervical adenocarcinoma, which account for about 15-20% of all cervical cancers (*9*). In addition, HPV-16 and HPV-18 also cause a vast amount of HPV-related cancers at other anatomic sites including the cervix, penis, vulva, vagina, anus, and oropharynx (*10*).

Epidemiological studies in multiple populations have indicated that persistent infection with a high-risk HPV type consistently precedes the appearance of precancerous changes, which include CIN 3, severe dysplasia or dyskaryosis, and carcinoma *in situ* (*4*). A prospective study has indicated that infection with carcinogenic HPV types is required for the development, maintenance and progression of these precancerous changes to invasive cancer (*4*). There are four steps by which HPV causes cervical cancer: HPV transmission, viral persistence, progression to precancer, and invasion (*4*). However, backward steps such as clearance of HPV infection and regression of precancer to normality (*4*) also occur, indicating interaction between HPV and the host immune response. In most infected women, the infection spontaneously resolves, and the infection even resolves in women who are at the most sexually active ages with very frequent infection with HPV. Only a very small fraction (about 10%) of women will develop viral persistence, and only some of those who are chronically infected with a high-risk HPV type will have a high risk of infection progressing to neoplastic lesions (*9*). The average total time from infection with a carcinogenic HPV type to the occurrence of invasive cervical cancer is 25-30 years or longer (*11*). HPV infection is basically a sexually transmitted disease. The most significant risk factors associated with HPV infection are related to individual's sexual behavior: starting sexual activity at an early age, a large number of sexual partners, sexual contact with high-risk individuals, and HIV infection; in contrast, male circumcision and the strict use of condoms are factors that protect women from HPV transmission (*6*). The main determinants of an HPV infection progressing to precancer and cancer are: the viral type, a persistent infection according to repeated examinations, integration of viral DNA into the host genome, and methylation of the HPV genome (*12*). Although the type-specific viral load per cellular unit appears to be associated with cervical cancer, a longitudinal study has not provided sufficient evidence that it can serve as a clinically useful predictor (*4*). However, HPV infection alone is not enough to trigger cervical cancer. Most women infected with HPV test negative within 2 years (*4*), while those with a persistent infection with high-risk HPV are at the greatest risk of developing cervical cancer, indicating that other viral factors or cellular events are required for progression from precancerous disease to cervical cancer.

The carcinogenic HPV types are evolutionarily related and belong to the genus *Alphapapillomavirus* with a small double-stranded circular DNA genome of approximately 8,000 pairs of bases. The HPV genome includes three regions: a long control region (LCR), an early region (E1, E2, E4, E5, E5, and E7), and a late region (L1 and L2). Eight genes are coded for by the HPV genome. The LCR involves in DNA replication, the early region regulates DNA replication and oncogenesis, and the late region produces viral capsule products (*13*). E6 and E7 are key oncoproteins with multiple cellular targets. During the process of HPV-induced carcinogenesis, E6 and E7 block apoptosis and deregulate the host cell growth cycle by binding to and interacting with p53 and retinoblastoma tumor suppression protein (pRB), respectively (*14*). In addition, these two proteins interact with various host cell targets, including those that regulate genomic instability (ATM, ATR and γ-tubulin), cell proliferation (E6AP, HDAC, P107, P130, and Cyclins), apoptosis (Caspase 8, BAX, BAK, IRF3, P600, and P48), and immortalization (TERT, MYC, and NFX123), thus interrupting multiple cellular pathways (*14*).

2. Alterations of the HPV genome and the host genome during the evolution of HPV as it induces carcinogenesis

DNA methylation within the HPV genome is one of the earliest and most common molecular alterations in multistep cervical carcinogenesis (*15*). Methylation of the HPV LCR and the *L1* gene increases with the severity of cervical dysplasia (*15*). A study has suggested that the status of HPV viral methylation may serve as a biomarker to help distinguish benign HPV infections from those that progress to precancer (*15*). An association between methylation of CpG sites in the HPV-16 *L1* gene and CIN2+ has been noted, suggesting that the detection of methylated viral DNA may distinguish CIN2+ from a high-risk HPV infection with no evidence of CIN2+ (*15*). Methylation profiles vary greatly among different genotypes. HPV-18 and HPV-45 are reported to exhibit a broader range and greater number of methylated CpG sites compared to HPV-16 and HPV-31 (*12*). Nevertheless, the association between viral methylation and precancer is a feature of

the four most important carcinogenic HPV types (HPV-16, 18, 31, and 45).

Parallel but distinct from HPV gene methylation, promoter hypermethylation of tumor suppressor genes in HPV-infected host cells is also an early and frequent epigenetic event (*16*). Promoter methylation in cervical precursors and invasive cancers has been noted for tumor suppressor genes in various cellular pathways, including genes involved in the cell cycle [*p16*, cyclin A1 (*CCNA1*), and the fragile histidine triad (*FHIT*)], cell adhesion [cell adhesion molecule 1 (*CADM1*) and E-cadherin (*CDH1*)], apoptosis (*DAPK*), cell signaling pathways [retinoic acid receptor-β2 (*RARβ2*) and Ras association domain family 1 isoform A (*RASSF1A*)], the Wnt/β-catenin pathway [adenomatous polyposis coli (*APC*)], the p53 signaling pathway (p73), and DNA repair [O^6-methylguanine-DNA methyltransferase (*MGMT*)](*16*). Moreover, methylation profiles differ for squamous cell carcinomas and adenocarcinomas. Studies have investigated the possibility that gene-specific hypermethylation profiles could serve as predictive biomarkers of cervical cancer risk, but their findings must be verified in prospective studies. In addition, folate is presumed to play a role in modulating the risk of cervical cancer by influencing promoter hypermethylation of tumor suppressor genes (*17*).

Moreover, HPV directly promotes genomic instability by integrating viral DNA into the host genome, which causes abnormal regulation of cell cycle control as well as epigenetic alterations that result in the silencing of tumor suppressor genes (*e.g.*, *APM-1*, and *CASZ1*) and that result in overexpression of oncogenes (*e.g.*, *MYC*) that facilitate the progression of cervical cancer (*18-20*). HPV integration into the host genome can be a driver mutation in cervical malignant transformation (*21*). A recent study reported that HPV-16 and/or HPV-18 integration into the host genome were associated with structural abnormalities and increased target gene expression (*22*). Both the integration rate and number of integration sites are reported to be higher in tissue from cervical carcinoma than in tissue from low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL), indicating a correlation between the level of HPV integration and the CIN grade (*23*). Based on these findings, the level of HPV integration could serve as a predictor of disease progression. The circular HPV genome is converted into a linear truncated DNA after integration (*18*). Breakpoints are distributed throughout the viral genome and are more likely to occur in *E1* than in *E2* but are less prone to occur in the LCR, while the viral *E6* gene may also be disrupted during certain events (*21*). Furthermore, significant enrichment of viral gene E7>E4>E5>E6 reads has been noted among cervical tumor samples, which is consistent with the known biological roles of the HPV genes in carcinogenesis (*24*).

3. APOBEC links immunity and viral infection during the evolution of papillomavirus as it drives the development of cervical cancer

Catalytic polypeptide-like apolipoprotein B mRNA editing enzymes (APOBECs) are a group of enzymes that catalyze the deamination of cytosine bases in nucleic acids, causing the conversion of target cytosine (C) to uracil (U) and consequently a change in the single-stranded DNA/RNA sequence (*25*). There are at least 11 members of the APOBEC family, including activation-induced cytidine deaminase (AID), APOBEC1 (A1), APOBEC2 (A2), APOBEC3 (A3), APOBEC3A (A3A), APOBEC3B (A3B), APOBEC3C (A3C), APOBEC3DE (A3DE), APOBEC3F (A3F), APOBEC3G (A3G), APOBEC3H (A3H), and APOBEC4 (A4) (*26*). The comprehensive biological functions and characteristics of the APOBEC family of proteins have been summarized elsewhere (*25*). APOBEC family members normally function as part of the innate immune system, which plays a key role in combating exogenous infection and especially viral infection. APOBEC expression is stimulated by viral infection *via* a complex network of innate immunity responses that involve components including Toll-like receptors, interferons, interleukins, and even the p53 protein (*27*). Previous studies have indicated that the APOBEC3 protein is a vital factor in HPV-driven carcinogenesis. APOBEC3 is presumed to play a role in inhibiting viral infection. APOBEC3A and APOBEC3C can enhance the ability of the human immune system to recognize HPV infection (*28*) while APOBEC3G can suppress the proliferation and invasion of cervical cancer cells (*29*).

3.1. *Host immune response during HPV-induced chronic inflammation*

The host immune response plays a vital part in infection with a high-risk HPV type. An effective immune response will facilitate spontaneous virus clearance, while a compromised one may facilitate the process of CIN progression and cervical carcinogenesis (*30*). Host immune responses, including humoral, cellular, and innate immunity, are considered to play important roles in the outcomes of HPV persistence and progression to cervical cancer. HPV may remain undetected for a very long time as infected cells evade the immune system. In addition, a persistent HPV infection stimulates immunotolerance of the host immune system and provides a microenvironment that facilitates further infection and progression of cervical lesions (*30*).

3.2. *Effects of HPV viral infection on APOBEC expression*

In HPV16 infection, levels of APOBEC3A and APOBEC3B mRNA are both reported to be up-regulated in low- and high-grade cervical lesions in

comparison to levels in normal tissues, and this up-regulation is possibly due to HPV16 oncoproteins E6/E7 (*31*). A previous study noted the expression of three genes of the APOBEC3A family, *hA3A*, *hA3B*, and *hA3H*, in skin keratinocytes, which are the main host cells for HPV infection (*32*). However, APOBEC3A expression was reported to be lower in cervical cancer tissues than in normal tissues (*33*). Changes in the level of APOBEC3A expression during different stages of cervical carcinogenesis suggest that APOBEC3A has antiviral and anticancer action. A study of precancerous lesions as well as cell lines found that APOBEC3A restricted HPV by editing HPV DNA (*34*). APOBEC3A can inhibit cervical cell proliferation, migration, and invasion and it can promote apoptosis depending on the level of cytidine deaminase activity (*33*). In addition, APOBEC3A restricts the functions of HPV16-E6, HPV16-E7 and HPV18-E6 through a cytidine deaminase-dependent mechanism, but it does not affect HPV18-E7. These findings indicate that APOBEC3A has antiviral and anticancer action by differentially inhibiting HPV E6 and E7 expression depending on the level of cytidine deaminase activity (*33*).

3.3. *Effects of APOBEC on the HPV genome and the host genome*

During the natural process of viral infection, the APOBEC3 protein may be involved in editing the HPV16 genome. APOBEC3 can gain access to the HPV genome during viral replication and induce C to U substitutions consistent with deaminase activity. Whether a viral infection triggers APOBEC3 mutagenesis is unclear, but a previous study detected APOBEC3 mutational signatures in the LCR of the HPV16 genome in CIN (*34*). A study noted a higher number of A/T mutations per sample in the *E2* gene in CIN3 compared to CIN1, suggesting that the APOBEC3 protein may induce clustered hypermutations in the LCR of the HPV16 genome (*35*). APOBEC3-induced mutations appear to accumulate with the progression of cervical lesions. Both C to T and G to A hypermutation patterns were detected in the coding strand of the *E2* gene of the HPV16 genome in CIN1 samples, while the C to T hypermutation was more prevalent in CIN3 samples (*33*). In cultured cervical keratinocytes, APOBEC3 subfamily proteins induce adenine/thymine clustered hypermutations in the *E2* gene of the HPV16 genome (*36*).

Besides targeting the viral DNA/RNA, the APOBEC family proteins also target host genomic DNA, generating enriched clusters of signature mutations in the genome (*37*). APOBEC family members can generate C-->T mutations and deaminate cytosines in the host genome. Results from next-generation sequencing studies have suggested that APOBECs can cause base substitutions in tumor genomes. Clustered mutations (termed kataegis) identified in breast cancer have a higher prevalence of the TCW motif (W refers to either A or T), which has more stringent APOBEC mutational specificity (*38,39*). Overexpression of the APOBEC3B protein is correlated with enrichment of the *APOBEC3B* mutation signature in the genomes of patients with cervical cancer (*27*). In-depth analysis of both whole-genome and exome sequencing data sets revealed a significant presence of APOBEC mutation patterns in cervical and head and neck cancers, both of which can be caused by HPV infection (*27*).

3.4. *APOBEC-mediated cancer-driver mutations in papillomavirus-driven tumorigenesis*

APBOEC may directly contribute to HPV-driven tumorigenesis by inducing mutations in putative cancer-driver genes. The APOBEC-mediated mutational process is reported to account for a large portion of major oncogenic *PIK3CA* mutations (helical domain mutations E542K and E545K) (*40,41*). Sequencing has fully characterized genomic alterations in HPV-associated cervical carcinomas (*22,42*). A study found that the APOBEC signature was significantly enriched up to 6-fold in most samples (150 out of 192) (*22*). In addition, the APOBEC mutation load is closely correlated with the total number of *PIK3CA* helical domain mutations per sample (*22*). Moreover, *PIK3CA* mutations often occur with mutations and deletions in *PTEN* (a well-established tumor suppressor gene), although not at a significantly higher rate (*22*). These findings highlight the potential role of APOBEC mutagenesis as a primary source of carcinogenic mutations in cervical cancer.

4. Conclusion

Chronic infection with HPV is one of the largest contributors to avoidable cancer deaths in China (*2*). The incidence of and the mortality rate for cervical cancer nationwide have significantly increased (*2*). A more worrying trend is that cervical cancer is occurring earlier and causing death in younger age groups in some developed urban areas (*43*). With the increasing prevalence of HPV infection especially in young women, combined with inadequate Papanicolaou (Pap) test screening and poor uptake of HPV vaccines, cervical cancer will continue to pose a huge public health burden to mainland China (*2,44*). Therefore, effective prevention and control strategies need to be identified. The standard treatment for cervical cancer is currently a combination of platinum-based chemotherapy and radiation, while few targeted therapies are available (*41*). Induction of cervical cancer by HPV represents an evolutionary process, which is modulated by viral, environmental, and host factors. The coexistence of HPV integration hotspots with scattered breakpoints and the strong tendency for HPV

to integrate into the functional regions of the human genome could be results of this evolutionary process. HPV may randomly integrate into the host genome based on genome accessibility from the beginning, but during the long-term course of carcinogenesis HPV may efficiently survey the human genome and select those integration sites that favor functional changes facilitating the malignant transformation of host cells (*21*). Key molecules and signaling pathways play crucial roles in milestone events during the carcinogenic process. Agents targeting special molecules and/or signaling pathways such as the PI3K signaling pathway may yield potential therapeutic benefits (*22*). The biological and/or immunological interactions between HPV and the host must be unraveled in order to develop better tools to control HPV infection and its malignant consequences. Moreover, revealing the genetic features of cervical cancer will enable personalized oncology, which promises to deliver tailored therapies to improve outcomes. Well-designed epidemiological studies must be conducted to sufficiently examine the importance of these events, to validate the potential of predictive markers and therapeutic agents, and to facilitate their subsequent use.

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