

Epstein–Barr Virus and Human Papillomavirus

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High-risk human papillomavirus (HR-HPV) is etiologically associated with the development and progression of cervical cancer, although other factors are involved. Overall, reports suggest a potential link of EBV to the development of cervical carcinomas in two possible pathways: (1) Infecting epithelial cells, thus synergizing with HR-HPV (direct pathway), and/or (2) infecting tissue-infiltrating lymphocytes that could generate local immunosuppression (indirect pathway). However, further studies are needed for a better understanding of the EBV/HR-HPV coinfection role in cervical carcinogenesis, in which in situ hybridization (ISH) and/or immunohistochemical methods are mandatory for discriminating the cell type infected by EBV.

Epstein-Barr virus

human papillomavirus

coinfection

cervical cancer

tissue- infiltrating lymphocytes

1. Introduction

The most important risk factor for cervical cancer development is infection with human papillomavirus (HPV) ^[1], with 99.7% of cervical carcinomas worldwide caused by high risk (HR)-HPV types, such as HPV16 or HPV18 ^{[2][3]}. While vaccines exist that protect against oncogenic HPV infection, global disparities still remain due to high costs ^{[4][5]}. However, HR-HPV infection is insufficient for cervical cancer development since low-grade squamous intraepithelial lesions (LSIL) usually regress to normal cells in cervical cytology or atypical squamous cells of undetermined significance (ASCUS). Only 3.6% of LSILs progress to high-grade squamous intraepithelial lesion (HSIL) ^[6], with a report of 50% regression in LSILs associated with HPV16 or HPV18 ^[7]. Accordingly, other host or environmental factors are necessary for cervical lesion progression, such as tobacco smoking (TS), oral contraceptive pills or immunosuppression, in particular infection with human immunodeficiency virus (HIV).

2. EBV Replication and Role in Cancer

EBV, also known as human herpesvirus 4 (HHV-4) is a gammaherpervirus that infects more than 90% of the human population worldwide ^[8]. It is characterized by a double-stranded DNA genome of 172 kb in length, surrounded by an envelope carrying various surface glycoproteins, with tegument proteins filling the space between the membrane and the inner icosahedral capsid ^[9]. EBV is related to some B cell-derived malignancies such as Burkitt's lymphoma (BL) and Hodgkin's disease (HD). Importantly, EBV is associated with some epithelial tumors, including undifferentiated nasopharyngeal carcinomas (NPCs) and a subset of gastric carcinomas (GCs) ^[8]. Figure 1 (left) shows the EBV genome organization with locations of latent genes.

Figure 1. Epstein-Barr virus (left) and human papillomavirus (right) genome organizations. Created by BioRender.com.

The mechanisms of EBV-mediated B-cell cancers are well known [10], although they are less understood in epithelial cells. In NPC cells, Epstein-Barr nuclear antigen 1 (EBNA1) has a key role in EBV persistency, decreasing p53 accumulation in response to DNA damage [11], whilst inducing epithelial mesenchymal transition (EMT), deregulating some related genes [12] and enhancing angiogenesis in vitro [13]. Latent membrane protein 1 (LMP1), another latent protein, impairs the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [14], activator protein 1 (AP-1) [15] and the Janus kinase/signal transducers and activators of transcription (JAK/STAT) [16] signaling pathways, leading to cell cycle disruption. Additionally, EBV-related epithelial tumors express BamHI-A rightward frame 1 (BARF1) [17], encoding a 220 amino acid lytic protein, secreted by EBV-infected epithelial cells as a soluble hexameric molecule (sBARF1) [18]. This viral protein hijacks human colony-stimulating factor 1 (hCSF-1), interfering with monocyte maturation [19] and impairing host immune responses against viral infections. It has been reported that BARF1 upregulates the expression of RelA and cyclin D1 and is able to reduce the cell cycle inhibitor p21WAF1 [20][21], promoting cell proliferation. Moreover, BARF1 activates the extracellular signal-regulated protein kinases 1 and 2 (ERK1/2)/c-Jun pathway [22] inhibiting apoptosis whilst increasing Bcl-2 and reducing both caspases and Bax [23]. Additionally, it inhibits interferon-alpha (IFN-α) production and release by mononuclear cells [24], impairing host immune responses. Interestingly, telomerase activation is observed in HPV-positive cervical cancer cells (HeLa) transfected with the BARF1 gene [25]. As BARF1 is expressed in EBV-associated NPC and GCs and not in lymphomas, BARF1 is considered an exclusive epithelial oncoprotein [25][26].

3. HPV in Cervical Cancer

HPV is a non-enveloped and exclusively intraepithelial virus, which comprises an 8 kb double-stranded circular DNA containing eight protein-coding genes divided into three major regions: Early, late and a noncoding region, known as the long control region (LCR). Early gene encoding non-structural proteins (E1 to E7) are involved in viral replication, transcription and transformation, while late transcribed genes encode for structural L1 and L2 proteins [27]. More than 210 HPV types have been identified by L1 sequencing, classified in HR-HPV (e.g., 16, 18 and 31) and low-risk (LR)-HPV types (e.g., 6, 7 and 11) according to the oncogenic potential [28][29]. Figure 1 (right) shows the HPV genome organization.

HR-HPV infection is etiologically associated with cervical carcinomas, anogenital and a subset of head and neck squamous cell carcinomas (HNSCCs). Integration of HR-HPV genomes into the host is an important hit, although not a requisite for epithelial carcinogenesis [30][31]. This is common in HSIL and cervical SCC compared with normal or LSIL tissues [32]. Moreover, HR-HPV (e.g., 16 and 18) integration in HSIL is frequently accompanied by chromosomal abnormalities [33], with E2 region loss during integration, leading to constitutive E6 and E7 protein expression [34]. E6 is a ~150 amino acid protein comprising two zinc finger binding domains connected by a 36 amino acid long-linker, and the carboxy terminal domain containing a PDZ-binding motif interacting with cell proteins [35]. E6 promotes loss of p53 via E6-associated protein (E6-AP)-mediated ubiquitination and proteasome degradation, inhibits apoptosis [36] and activates Mitogen-activated protein kinase (MAPK) and the mechanistic

target of rapamycin complex 1 (mTORC1) pathways [37][38]. Additionally, E6 targets the pro-apoptotic proteins Bak for degradation [39] and others such as the Fas-associated protein with death domain (FADD) and caspase-8, disrupting the apoptotic program [40]. Likewise, E7 is a 100 amino acid protein comprising three conserved regions denoted CR1, CR2 and CR3, with CR3 containing two CXXC motifs separated by 29 or 30 residues. Moreover, the E7 carboxyl terminal domain contains a zinc-binding motif mediating interaction with cellular proteins [41]. E7 targets retinoblastoma protein (pRb) for ubiquitination, leading to E2F transcription factor release, allowing cell entry to S-phase [42]. Both E6 and E7 interact with c-Myc inducing human telomerase reverse transcriptase (hTERT) promoter activation and hTERT expression, enabling cell evasion of senescence [43][44]. E6 and E7 also upregulate expression of EMT markers such as N-cadherin, Fibronectin and Vimentin, increasing cell migration and invasiveness [45]. Moreover, E6 and E7 inhibit interferon (IFN) antiviral activity and decrease tumor necrosis factor alpha (TNF- α) and (interleukin-1 beta) IL-1 β secretion by macrophages, enabling immune evasion [46].

HR-HPV infection is insufficient for cervical carcinogenesis and involvement of other cofactors is essential. While factors involved in HR-HPV integration into the host genome are unclear [47], a prerequisite is DNA damage [48], TS being a very important factor for cervical cancer development [49] by activating the HPV16 p97 promoter and leading to E6 and E7 overexpression [50]. Moreover, HPV16 E6 and E7 collaborate with TS, increasing the tumor properties of epithelial cells [51][52], although other potential cofactors such as chronic inflammation and bacterial or viral coinfection are also suspected.

4. Mechanisms of HPV/EBV-Mediated Cervical Carcinogenesis

Experimental approaches evaluating molecular mechanisms involved in EBV/HR-HPV coinfection are limited. However, EBV LMP1 in combination with HPV16 E6 viral proteins in transformed mouse embryonic fibroblasts (MEFs) reduces components of DNA damage response (DDR) such as p53, pRb and p27, whilst increasing checkpoint kinase 1 (CHK1), NF- κ B signaling, v-akt murine thymoma viral oncogene (Akt) and MAPK signaling [53][54]. In addition, LMP1 induces down-regulation of E-cadherin expression [55] and also regulates TWIST [56] and SNAIL [57] transcription factors and others related with cell motility. Moreover, LMP1 and E6 co-expression induces cell proliferation, resistance to apoptosis, anchorage-independent growth and tumor-formation ability in nude mice compared with single expression of EBNA1 or E6 [36]. In EBV-infected NPC cells, EBNA1 plays a role in EMT through inhibition of both microRNA (miR)-200a and -200b expression, while it up-regulates the expression of *ZEB1* and *ZEB2*, their target genes [12]. Interestingly, double expression of LMP1 and HR-HPV E6 relates with a more aggressive form of malignant tumor such as breast adenocarcinoma [58] and cervical SCC [59]. Thereby, in the case of EBV-associated GCs, EBNA1 may induce constitutive and also IFN γ -inducible programmed death-ligand 1 (PD-L1) expression in EBV-infected epithelial- cells [60]. In HPV+ HeLa and SiHa cervical cells, transfection with a small interfering RNA (siRNA) for Myc knock down was able to reduce the *hTERT* promoter activity [61]. HPV16 E6 activates *hTERT* gene transcription through induction of c-Myc, which is overexpressed in cervical carcinomas [62][63]. Moreover, hTERT activation in BARF1-transfected PATAS monkey kidney cells was accompanied by up-regulation of c-Myc, while in HeLa cells BARF1 induces activation of telomerase binding directly to initiator

elements in the *hTERT* promoter region [25]. Alternatively, both HPV18 E6 and E7 oncoproteins are necessary to increase EBV genome maintenance in normal oral keratinocytes (NOKs) and to induce the reactivation of the EBV lytic program in suprabasal layers of oral epithelial from an in vitro organotypic raft culture model [64]. However, a significant reduction in EBV immediate early (BZLF1, BRLF1) and early (BALF5, BMRF1) gene expression with increased expression of EBER1 was evidenced in HPV+/EBV+ human foreskin keratinocytes (HFK) compared to that in HPV-/EBV+ rafts [65]. In cervical cells, increased levels of EBER1 may contribute to the transition from inflammation to oncogenesis of HPV-associated cervical cancer by modulating innate immune responses [66]. In addition, LMP1 reduces the presence of HPV16 with no expression change in the EBNA1 and EBNA2 latent genes, suggesting that EBV latency is favored over lytic replication in HPV16+ cells. However, LMP1 is mostly expressed in B-cell lymphomas, lymphoproliferative disorders and NPC [67], but less in cervical and GCs [68][69]. In uterine cervix, latency III EBV infection is increased in CIN and cervical SCC compared with non-malignant samples [68], conferring a long-term persistence of EBV infection in malignant cells. Furthermore, reduced EBV replication mediated by HPV16 E7 is related to retarded expression of some markers related with early epithelial cell differentiation [65]. Similarly, cervical SCC EBV/HR-HPV coinfection is associated with decreased cell differentiation [59], closely related with a more aggressive tumor. Additionally, NOKs and FaDu hypopharyngeal carcinoma cells coinfecting with EBV and HR-HPV show increased invasiveness in the lysophosphatidic acid (LPA) presence (glycerophospholipid able to stimulate cell migration) compared to EBV-/HR-HPV- and EBV+/HR-HPV-cells [70], resembling the effects of coinfection in cervical SCC [59]. According to our knowledge, the levels of BARF1 in cervical cancer have been examined in only one study, which reported 27% detection in tumors from Algerian women [71]. As previously stated, this protein has been suggested as an epithelial EBV oncogene, which is expressed in a cell differentiation-dependent manner [72]. Due to this lytic protein being expressed in a majority of EBV+ NPC and GC cells, the possibility that this protein is involved in EBV+ cervical carcinomas, working in both oncogenic process and immune evasion is plausible. Considering that EBV infection in normal epithelial cells is exclusively lytic [73][74], an interesting point is the establishment of EBV latency in epithelial cervical cells. In this respect, it has been suggested that previous DNA damage in cells is a requisite [75]. Thus, we can propose a scenario in which previous HPV infected and subsequently DNA-damaged cells (e.g., by HPV E7) are particularly susceptible to EBV latency establishment. Moreover, we can speculate on the possibility that HPV is involved in the activation of the EBV abortive lytic cycle, promoting expression of some lytic genes, such as Zebra or Rta, which has been reported to be important in EBV-mediated carcinogenesis. A hypothetical model in which HPV infection favors EBV latency establishment in epithelial cervical cancer cells is shown in Figure 2.

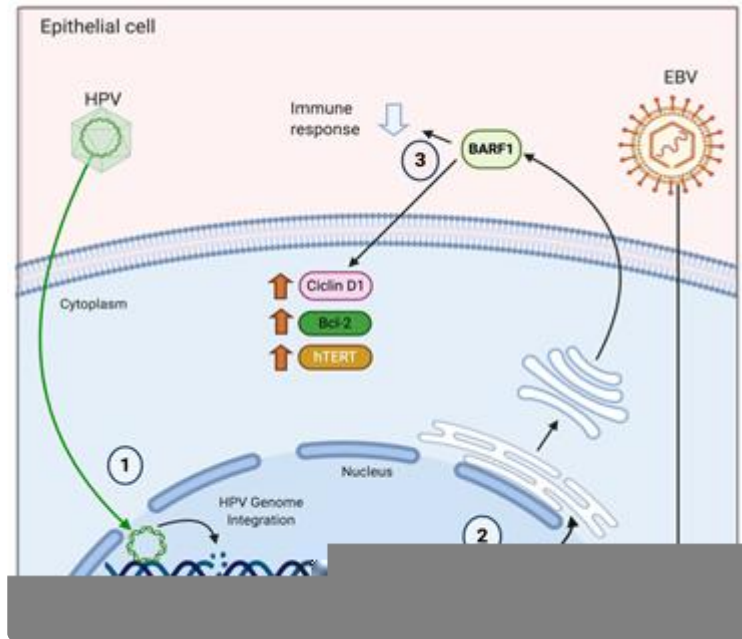


Figure 2. A hypothetical model of HR-HPV/EBV interaction in cervical epithelial cells. **1.** HR-HPV infection and viral integration promotes DNA damage and genomic instability in cervical cells; **2.** DNA damage promotes the establishment of EBV latency (I/II) with potential expression of some lytic genes such as BARF1 (abortive lytic expression); **3.** BARF1 (and other viral oncogenes) promotes oncogenic changes and immune evasion, cooperating with HR-HPV. Created by BioRender.com.

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