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REVIEW PAPER

Effects of β-HPV on DNA damage response pathways to drive carcinogenesis: a review

Danyal Tahseen[1] · Peter L. Rady[1] · Stephen K. Tyring[1]

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Abstract
The DDR is a complex signaling network responsible for the preservation of genomic integrity. Beta human papillomaviruses (β-HPVs) are able to destabilize the host genome by attenuating the DDR machinery at the molecular scale following expression of the oncogenes E6 and E7. In the event of β-HPV infection, the E6- and E7-mediated inhibition of the DDR enhances the oncogenicity of UV-induced mutations to enable carcinogenesis in an otherwise immunocompetent host, marking an important mechanistic divergence from the alpha genus of HPVs. In this review, we summarize recent updates to build upon the 'hit-and-run' hypothesis of β-HPV pathomechanism and highlight strain-dependent variations. Simultaneously, we illuminate points within the β-HPV–DDR interface that may unravel new insights for HPV viral genetics, genus-specific mechanistic models, and developments in targeted molecular therapy of β-HPV-related cancers.

Keywords β-HPV · DNA damage response · Virus–host cell interactions · Non-melanoma skin cancer

Introduction

Human papillomavirus (HPV) is a family of small, non-enveloped double-stranded DNA viruses that consists of five genera (alpha, beta, gamma, nu, and mu) [1, 2]. While the role of genus alpha HPVs in the tumorigenesis and tumor progression of oropharyngeal and cervical cancers is well characterized, the role of genus beta HPVs (β-HPVs) in non-melanoma skin cancers (NMSCs) is less certain. β-HPVs have been heavily implicated in newly diagnosed cases of NMSCs, particularly cutaneous squamous cell carcinomas (cSCCs) [3–6]. Specifically, the β-HPV subtypes 5, 8, 15, 17, 20, 24, 36, and 38 contribute to the initiation of cSCCs [4, 7]. This etiological association is garnering attention due to its abundance/prevalence in the skin and hair follicles of immunocompetent individuals, who are not typically considered at risk for HPV infection [6, 8–10].

β-HPV replication has been linked to multiple mechanisms of cellular perturbation including apoptosis, cell cycle dysregulation, and transcriptional regulation. Among these, β-HPV's disruption of the DNA damage response (DDR) provides a compelling mechanistic model to reconcile the expedited mutagenesis seen in β-HPV lesions and their presentation in immunocompetent individuals [9, 11–14]. Abrogation of the complex DDR network compromises the cell's natural ability to repair genotoxic insults [15]. Emerging models of β-HPV carcinogenesis have emphasized its cooperativity with external-DNA damaging agents such as UV exposure (particularly UV-B) [9, 13, 16]. On a molecular scale, the oncogenic potential of β-HPVs is attributed to the oncoproteins E6 and E7, with minor contribution from E5, which orchestrate uninterrupted accumulation of mutagenic DNA damage without triggering cellular apoptosis [14, 17]. Importantly, β-HPV is associated with DDR attenuation in contrast to the 'activate-and-redirect' model used to describe α-HPV's DDR modulation strategy [18]. *In-vivo* models of β-HPV infection show repeated signs of promoting the S-phase, where homologous recombination becomes the preferred DDR pathway [18]; we debate any implications this nuance may hold in the grand scheme of β-HPV oncogenesis.

Recent evidence has situated the β-HPV–DDR interface as a high-priority therapeutic target. The popular "hit-and-run" hypothesis posits that β-HPV is only needed for the early stage of carcinogenesis (tumor initiation), after which

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✉ Stephen K. Tyring
stephen.k.tyring@uth.tmc.edu

[1] Department of Dermatology, McGovern Medical School at UT Health Science Center, Houston, TX 77030, USA

the compromised DDR is sufficient to support malignancy without viral gene expression [10, 17]. This suggests a very narrow window to initiate antiviral therapy [9, 19]. As such, characterization and identification of therapeutically relevant targets within the β-HPV–DDR interactome is an emerging frontier in the literature [11, 20]. Development of β-HPV vaccines informed by this theoretical framework is yet to occur [21], although preclinical studies targeting DDR machinery with poly(ADP-Ribose) polymerase (PARP) inhibitors are encouraging [22–24]. This review summarizes recent molecular insights regarding how β-HPV oncoproteins manipulate DDR pathways to drive carcinogenesis in immunocompetent hosts.

Brief overview of DDR in the β-HPV viral life cycle

DDR is a complex signaling network directed to preserve host genomic integrity in response to an array of exogenous and endogenous stressors. Depending on the insult, DDR regulation is predominantly regulated by two major PI3 kinase-related kinases (PIKKs): ataxia-telangiectasia mutated (ATM) and ATM- and Rad3-related (ATR) [15]. ATM is recruited to double-stranded breaks (DSBs) through the MRE11-RAD50-NBS1 (MRN) complex [25]. Meanwhile, ATR is recruited to RPA-coated single-stranded DNA (ssDNA) in response to DNA replication stress [25].

ATM and ATR activate cell cycle checkpoints by phosphorylating the checkpoint kinases Chk1 and Chk2, respectively. Chk1/Chk2 activation induces the remainder of the DDR pathway while pausing cell cycle progression [26]. In a carcinogenic context, dysregulation of cell cycle checkpoints not only enables hyperproliferation but also more specific to the DDR allows exacerbation of milder types of DNA damage to more mutagenic and dangerous forms such as DSBs. P300 is a transcriptional cofactor for BRCA1 and BRCA2 which direct homologous recombination (HR), a key mechanism for faithful DSB repair [27–29]. Appropriation of the cell's HR mechanism both accelerates high-fidelity viral replication and destabilizes host DNA to allow accumulation of oncogenic mutations [27–29]. As such, targeting the ATM and ATR pathways is central to β-HPV's infection strategy.

Role of UV exposure in the β-HPV–DDR interface

Cancer-associated cutaneous β-HPVs attenuate the DDR, a mechanism with important functional consequences for viral propagation by way of delaying repair of UV-induced DNA damage and increasing risk of progression to oncogenesis [30, 31]. In fact, UV-dependent carcinogenesis appears to be a unique feature in β-HPV compared to other HPV genera, and may help understand the abundance of β-HPV-related NSMCs (e.g., cSCC) in otherwise healthy individuals. This coincides with increased β-HPV loads being detected in sun-exposed skin areas, as UV exposure might induce "localized" immunosuppression at the affected skin region in an otherwise immunocompetent host [9, 30].

β-HPVs may directly inhibit host DDR factors to increase the frequency of UV-induced DSBs. Some UV-induced DSBs may be evolutions of less mutagenic precursors such as UV-induced cyclobutane pyrimidine dimers (CPDs) [31, 32]. In β-HPV-5 and β-HPV-8, both the repair of CPDs (ATR dependent) as well as the repair of DSBs (ATM, BRCA1 and BRCA2 dependent) are significantly delayed [12, 31–33]. Other forms of UV-induced genomic insults are 'transition' mutations which may interrupt critical tumor suppression genes such as *TP53*, further accelerating tumor initiation [34]. The attenuation of DSB repair, a consequence of β-HPV/UV cooperativity, accelerates tumor initiation as well as host genome destabilization. Now we will discuss in detail the mechanisms by which the E6 and E7 oncoproteins encoded by the β-HPV genome (Fig. 1) support UV-induced DNA damage.

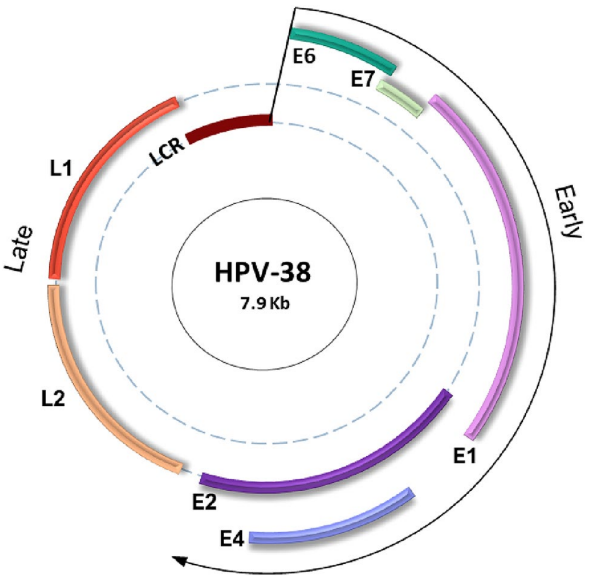

Fig. 1 A schematic representation of the dsDNA genome organization of HPV-38, a member of cancer-associated β-HPV viruses. Three functional regions are depicted: the early region (oncoproteins E1, E2, E4, E6, E7), the late region (capsid proteins L1–L2), and a long control region (LCR). Omission of E5 oncogene from the β-HPV genome represents a characteristic distinction compared to the α-HPV genome [35]

Role of E6 in the β-HPV–DDR interface

The E6 oncoprotein of β-HPVs can directly impair DNA repair factors as well as disable cellular apoptosis in response to DNA damage. However, the hypothesized mechanisms executing these functions vary by strain.

p300 pathway, ATM/ATR, BRCA1/2

E6 homologs in β-HPV-5, 8, and 38 bind acetyltransferase p300 strongly enough to disrupt the DDR pathway at various levels, delaying and diminishing the activation of ATM, ATR, BRCA1, and BRCA2 [35]. Given that BRCA1 and BRCA2 are associated with the HR subset of DNA repair machinery, their inhibition secondary to p300 destabilization means that the cell loses the ability to faithfully repair UV-induced DSBs and may be forced to rely on more error-prone repair pathways [18, 31], a projection that would ultimately favor β-HPV carcinogenesis by compromising host genomic integrity.

NOTCH pathway

In β-HPV-5 and 8, E6 demonstrates MAML1-mediated inhibition of the tumor-suppressive NOTCH signaling pathway [36]. Inhibition of NOTCH simultaneously removes negative regulation of the ATM arm of DDR and prolongs the S-phase to allow maximal accumulation and redirection of HR-specific ATM machinery (such as BRCA1 and BRCA2) [37, 38]. Thus, the elongation of S-phase amplifies the effects of DDR impairment to boost HPV carcinogenesis [39–41]. Although further studies are needed to understand molecular mechanisms of NOTCH signaling before attempting clinical trials, recent literature has discussed NOTCH-activating agents as theoretically attractive options for cSCC therapy as they may restore the cell's ability to recognize accumulating DNA damage [42].

TGF-β pathway

Similar to NOTCH inhibition, an analogous—and possibly complementary—mechanism of DSB repair attenuation has been identified in E6-induced disruption of the transforming growth factor-beta (TGF-B) pathway [41, 43]. β-HPV-5 and 8 E6 bind the transcription factor SMAD3, abrogating tumor suppressive effects of the TGF-β pathway and ultimately inhibiting repair of UV-induced DSBs [41, 43–46]. Additionally, TGF-β inhibition enables early progression from G1- into S-phase, where HR becomes the cell's repair pathway of choice.

Cell cycle regulation and DNA repair pathway choice

Comparing E6-mediated effects on p300, NOTCH, and TGF-β, all three hypotheses of DDR modulation cooperate with UV irradiation, favor severe forms of DNA damage (DSBs), and attenuate DSB repair pathways within the DDR. While both HR and non-homologous end-joining (NHEJ) are capable of DSB repair, it merits noting that E6 favors S-phase elongation (NOTCH inhibition) and/or early S-phase entry (TGF-β inhibition), and HR is the predominant repair pathway during the S-phase [18, 30, 38]. Simultaneously, E6 employs p300 degradation to ultimately attenuate critical HR factors (BRCA1 and BRCA2) [18, 30]. One possibility to reconcile these observations is that E6 influences DNA repair pathway choice by a complex sequential mechanism, where E6 first creates conditions for maximal expression of HR factors (BRCA1 and BRCA2)—the cell's most high-fidelity repair armament—only to then degrade the HR factors once they are exposed. It follows that E6′s apparent downregulation of HR may serve advantageous to β-HPV pathogenesis by maximizing host genome destabilization, although further delineation using *in-vivo* models is needed.

hTERT stabilization

A more controversial mechanism of DDR attenuation described for E6 in β-HPV-5, 20, 22, and 38 is hTERT stabilization [11, 47]. hTERT activity prevents unstably short telomeres, which may theoretically support destabilization of host genome by allowing unchecked proliferation of older mutation-rich cells [47]. On the other hand, this may also stabilize the genome of newer cells which would oppose the β-HPV oncogenic strategy [11].

Apoptotic pathways

Among its apoptosis-mediated mechanisms of DDR modulation, E6 can degrade the pro-apoptotic factor BAK, a function highly conserved across the β-HPV genus [48–51]. E6-mediated BAK degradation is amplified following UV-induced DNA damage in order to evade cellular apoptosis and permit uninterrupted viral replication within an "immortalized" yet genetically unstable host cell. Similarly, E6 inhibits apoptosis by degrading p53 (via E6AP in β-HPV-49; via HIPK2 in β-HPV-23) or altering the p53 transcription profile (β-HPV-17, 38, 92) to attenuate downstream factors relevant to DDR [11]. Functionally, apoptotic suppression serves to increase the cell's tolerance to the ongoing DSB accumulation potentiated by E6-mediated inhibition of p300, NOTCH, TGF-β. Future

studies may consider if apoptotic suppression has a role in hTERT-mediated DDR attenuation.

Role of E7 in the β-HPV–DDR interface

Cell cycle regulation and DNA repair pathway choice

β-HPV E7 destabilizes the cell cycle regulator pRb, prematurely driving the cell into the S-phase, where HR theoretically becomes the preferred mode of DSB repair [11, 18]. Molecular evidence of repair pathway choice manipulation during β-HPV pathogenesis is not yet established, although E7′s subversion of ubiquitin ligase RNF168 seems to favor a similar outcome. Given that RNF168 normally favors non-homologous end-joining of DNA breaks, inhibition of RNF168 during β-HPV infection may isolate HR as the cell's only remaining choice for DNA repair during an already elongated S-phase [52]. The strategic implications of HR promotion in β-HPV pathogenesis merit closer investigation.

p53 pathways

β-HPV-38 E7 inhibits tumor suppressor p53 as well as p53-dependent transcriptional targets in DDR pathways. Mechanistically, E7 achieves p53 inhibition by harnessing transcriptional and post-translational mediators to support accumulation of ΔNp73α, a p53-antagonist [13, 53]. However, the cellular events underlying E7′s modulation of p53-related DDR genes are not well understood. Speculation has been directed towards Polη (TLS pathway) and XPC (NER pathway) as relevant targets [54–56].

PTPN14 pathways

Preliminary evidence suggests that E7 from β-HPV-8, 25, and 92 interacts with tumor suppressor PTPN14, but the relevance of E7/PTPN14 interaction in β-HPV carcinogenesis remains elusive [11]. Yap1, a regulatory substrate of PTPN1 within the Hippo pathway, is important for the onset of apoptosis when intracellular DNA damage (e.g., UV-induced) is detected [57]. Provided that evading cellular detection of UV-induced mutations is conducive to the completion of β-HPV's life cycle, disconnection of the PTPN14-dependent response may be a pertinent target for future studies of β-HPV pathogenesis.

Conclusion and suggested future directions

The increasing burden of β-HPV tumors among immunocompetent individuals is concerning. Motivated to explain this peculiar association, recent molecular investigations of β-HPV carcinogenesis have emphasized the virus's cooperativity with UV irradiation and apparent "hit-and-run" mechanism. Both these observations coincide with current descriptions of the β-HPV–DDR interface.

Why may DDR modulation serve advantageous to β-HPV pathogenesis? Primarily, attenuating the DDR allows β-HPV to promote its own replication, with mutagenesis and carcinogenesis being by-effects that may not directly contribute to the β-HPV life cycle but contribute significantly to the pathogenic outcome. Normally, viral replication would activate an intact DDR, resulting in a slow-down of host cell replication. To bypass this in the infected cell, β-HPV targets the DDR in order to promote its own replication. The by-product of β-HPV's ability to compromise the DDR is that the modified cellular environment maximizes the frequency and severity of UV-induced mutations, while destabilizing the host genome. After a certain threshold of DNA damage, tumor progression can be sustained even without β-HPV gene activity.

E6/E7 oncoproteins are critical players in the complex β-HPV–DDR interface, as they directly mediate DDR perturbation, subsequently facilitating viral propagation and the by-effect of tumorigenesis. Both E6 and E7 perturb the DDR proteome extensively, employing a blend of distinct as well as overlapping mechanisms (Table 1).

Effects of E6 on the p300, NOTCH, and TGF-β pathways represent the clinicopathologic basis for synergism between UV irradiation and β-HPV, which in turn orchestrates accumulation of DNA damage at the expense of host stability. Delineating subsequent steps in this sequence of events may yield important prognostic markers preceding the manifestation of cutaneous symptoms in β-HPV cancer patients, so that early intervention before the viral-independent stage of tumor progression is possible. Combined effects of E6 and E7 on cell cycle regulation support tumorigenesis by altering the concerting field within which DDR machinery is released. Multiple lines of mechanistic investigation reveal instances of S-phase modulation (i.e., limiting DNA repair pathway choice) as well as inhibition of specific repair pathways critical for DSB resolution (i.e., BRCA1/2 which direct DSB repair via HR) (Fig. 2). Collectively, these findings suggest β-HPV's ability to cultivate a cancer proteomic landscape that minimizes resistance against the most severe forms of DNA damage. Validation/Characterization of these molecular associations in the setting of symptomatic β-HPV infection may open new directions for prognostic estimation and early intervention.

Over recent years, several therapeutic investigations for HPV-driven cSCC tumors have indicated potential for non-coding RNA (ncRNA) agents targeting PIWI proteins considered tumorigenic markers in cSCC [58]. Thus far, successful demonstrations in cSCC have been nearly exclusive to α-HPV-related cSCCs (i.e., HPV16), and their

Table 1 Summary of mechanisms used by major cancer-associated β-HPVs and oncoproteins to inhibit the DNA damage response, leading to carcinogenesis

	Beta-HPV-5 and 8	Beta-HPV-38
Overall strategy of viral DDR modulation	Weaken host cell's DNA damage response (DDR) to induce genomic instability Increase oncogenic potential of UV-induced mutations (progression to DSBs) Delay DSB repair	
Roles of E6 in DDR modulation	Destabilize p300 pathway *Inhibit ATM, ATR, BRCA1/2 (HR) to delay DSB repair *Inhibit NOTCH *Inhibit TGF-β Degrade apoptotic factors (BAK) Limit DNA repair pathway choice? Promote S-phase of cell cycle	Destabilize p300 pathway *Stabilize hTERT to activate telomerase Degrade apoptotic factors (BAK; *p53-dependent factors) Limit DNA repair pathway choice? Promote S-phase
Roles of E7 in DDR modulation	Inhibit p53 Limit DNA repair pathway choice? Promote S-phase of cell cycle Inhibit RNF168	Inhibit p53 Limit DNA repair pathway choice? Promote S-phase of cell cycle Inhibit RNF168

Asterisks (*) represent strain-specific mechanisms

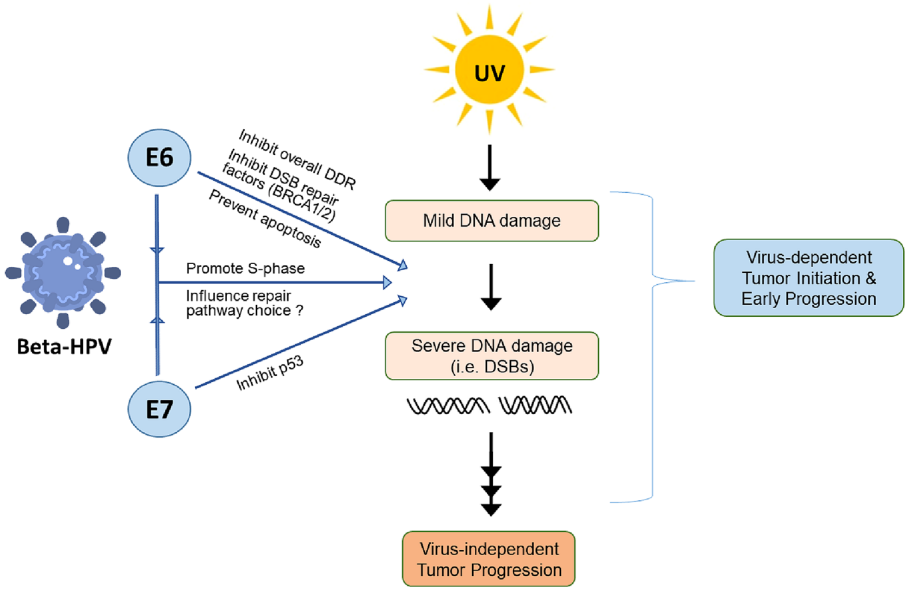

Fig. 2 Proposed theoretical framework for relationships between UV irradiation and β-HPV-induced changes in cell cycle regulation, apoptosis, and DNA repair machinery, as pertinent to maximizing accumulation of mutagenic double-stranded breaks (DSBs)

applicability is contingent on viral genome integration [58]: a phenomenon central to α-HPV carcinogenesis, but yet to be described in β-HPV models. While this mechanistic divergence between the genera may be annulled with future updates, it appears consistent with their respective DDR modulation mechanisms. Where α-HPV oncoproteins activate the DDR and subsequently appropriate its factors to aid integration into host DNA, our review of the β-HPV–DDR interface supports a model where DDR factors are inhibited without evidence of redirection [10, 55]. A framework of prolonged DDR inhibition seems conducive to β-HPV's overall infection strategy. Without the need to preserve host genome integrity for viral integration, sustained DDR suppression may afford β-HPV freedom to haphazardly accumulate UV-induced mutations and—consistent with the "hit-and-run" mechanism—accelerate tumor progression towards a virus-independent state. Considering the growing associations of cSCC tumors reflecting *beta* HPV types, particularly among immunocompromised patients, future therapeutic investigations must consider genus- and strain-specific mechanistic heterogeneity when identifying targets.

From a viral genetics perspective, exploring the functional implications of the E5 oncogene, which is absent in β-HPV but recently gaining significance in α-HPV tumorigenesis [59, 60], is warranted for delineation of genus-specific mechanistic models. With β-HPV's molecular effects

on the DDR aligning neatly with the clinical behavior of β-HPV-positive tumors, closer attention to the β-HPV–DDR interface in context of the larger virus–host interactome may streamline chemotherapeutic investigation.

Finally, it may serve useful to contextualize future research findings about β-HPV pathogenesis back within the overarching "hit-and-run" mechanistic framework, so that subsequent iterations of the model can be updated or redirected in a consistent manner. As a conceptual bridge to further consolidate how the many virus–host cell interactions reviewed here build upon the "hit-and-run" framework, exploring why cSCC tumors seem to 'lose' β-HPV genomes during the course of UV-induced clonal expansion could constitute an illuminating next step. For example, it is possible that the functional roles of eliminated β-HPV genes (perhaps certain transcription factors) may become redundant following abrogation of the host cell's DDR factors; thus, preserving those components may become too energetically costly or perhaps no longer necessary for sustaining the remainder of the viral life cycle.

Author contributions All authors contributed in producing the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The manuscript adheres to all ethical and legal guidelines.

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