Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Review:

DNA damage response is hijacked by human papillomaviruses to complete their life cycle

Shi-yuan HONG

(*Department of Microbiology-Immunology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA*)

E-mail: Shiyuan-hong@northwestern.edu

Received July 4, 2016; Revision accepted Nov. 14, 2016; Crosschecked Feb. 8, 2017

Abstract: The DNA damage response (DDR) is activated when DNA is altered by intrinsic or extrinsic agents. This pathway is a complex signaling network and plays important roles in genome stability, tumor transformation, and cell cycle regulation. Human papillomaviruses (HPVs) are the main etiological agents of cervical cancer. Cervical cancer ranks as the fourth most common cancer among women and the second most frequent cause of cancer-related death worldwide. Over 200 types of HPVs have been identified and about one third of these infect the genital tract. The HPV life cycle is associated with epithelial differentiation. Recent studies have shown that HPVs deregulate the DDR to achieve a productive life cycle. In this review, I summarize current findings about how HPVs mediate the ataxia-telangiectasia mutated kinase (ATM) and the ATM- and RAD3-related kinase (ATR) DDRs, and focus on the roles that ATM and ATR signalings play in HPV viral replication. In addition, I demonstrate that the signal transducer and activator of transcription-5 (STAT)-5, an important immune regulator, can promote ATM and ATR activations through different mechanisms. These findings may provide novel opportunities for development of new therapeutic targets for HPV-related cancers.

Key words: Papillomavirus; DNA damage; Amplification; Differentiation; ATM/CHK2; ATR/CHK1; STAT-5
http://dx.doi.org/10.1631/jzus.B1600306 **CLC number:** R737.33

1 Introduction

DNA damage occurs naturally in cells and is associated with intrinsic reagents such as reactive oxygen species (ROS) or extrinsic agents such as ultraviolet (UV), ionizing radiation (IR), and chemotherapeutic drugs. The process begins with an alteration in the structure of DNA through formation of single and double DNA breaks, as well as other changes. In response to DNA damage, cells signal through a complex network. This response plays important roles in processes such as genome stability, tumor transformation, and cell cycle regulation (Matt and Hofmann, 2016). To maintain genome stability, cells must repair damage-induced DNA lesions. If the damage cannot be fixed, cells activate cell cycle check points to trigger cell death. Previous studies have shown that deregulation of the DNA damage response (DDR) can contribute to the development of various cancers such as hereditary non-polyposis colorectal cancer, non-small-cell lung cancer, breast cancer, and ovarian cancer, as well as other cancer-causing conditions such as Fanconi anaemia (FA), xeroderma pigmentosum, and ataxia telangiectasia (Lord and Ashworth, 2012; Sperka *et al.*, 2012; O'Connor, 2015; Seebode *et al.*, 2016). Many small molecule modulators targeting the DDR have been proposed as potential therapeutic treatments against cancers ranging from acute myeloid leukaemia to lung squamous cell carcinoma, as well as cervical squamous cell carcinoma (Pearl *et al.*, 2015).

Worldwide, cervical cancer is the fourth most common cancer in women and the second most frequent cause of cancer-related death. Human

ORCID: Shi-yuan HONG, http://orcid.org/0000-0002-0319-5208

papillomaviruses (HPVs) are the causative agents of cervical cancer as well as other anogenital cancers (Zur Hausen, 2002). There are more than 200 types of HPVs. Around 40 of them infect the genital tracts and are sexually transmitted. HPVs can be classified as high-risk or low-risk according to their association with cancers. Infection by low-risk HPVs can lead to cutaneous lesions or benign mucosal lesions while high-risk HPV infection may develop into anogenital or oropharyngeal cancers (Zur Hausen, 2009; Doorbar *et al.*, 2012). Evidence suggests that persistent infection of high-risk HPVs causes genetic instability (Ho *et al.*, 1995; Herrero *et al.*, 2000) and DNA damage repair machinery is utilized by HPVs for productive viral replication (Hong and Laimins, 2013b; Galloway and Laimins, 2015; McKinney *et al.*, 2015). The purpose of this review is to understand better how HPVs employ the DDR, especially ataxia-telangiectasia mutated kinase (ATM)/ATM- and RAD3-related kinase (ATR) signaling, in their life cycle. Before describing what is known about the pathway, I will summarize the cellular pathways involved in the DDR and give a general description of mechanisms that have been reported to be involved in regulating the productive life cycle of HPVs. Then I will discuss the relationship between the DDR and the HPV viral life cycle in detail, including the roles of the signal transducer and activator of transcription-5 (STAT-5).

2 DNA damage response

2.1 Significance and classification of DNA damage response

It has been estimated that up to 200 000 DNA damage lesions occur naturally in each cell every day (Atamna *et al.*, 2000). The causes of DNA damage can be either endogenous or environmental. Endogenous causes of DNA damage include replication errors, unrepaired single strand lesions, and base deamination or loss (Curtin, 2012). Environmental causes result mainly from exposure to damaging agents, including UV, IR, ROS, *S*-adenosyl methionine, dietary nitrosamines, and tobacco. In response to DNA damage, cells mount collective cellular events such as cell-cycle arrest, regulation of gene expression and DNA replication, activation of DNA damage repair, and cell fate decisions (Matt and Hofmann, 2016). Proper DNA damage repair is necessary for genome stability, prevention of transformation, and tumor suppression. Deregulation of the DDR leads to many clinically relevant diseases such as premature aging, neurodegenerative disorders, and cancer formation (Jackson and Bartek, 2009).

DNA damage often results in DNA mutations, crosslinking, and single-strand breaks (SSBs) as well as double-strand breaks (DSBs). Damaged cells activate various pathways to repair these lesions, including base excision repair (BER), nucleotide excision repair (NER), mismatch repair, non-homologous end joining (NHEJ), homologous recombination repair (HRR), and interstrand crosslink repair (Curtin, 2012). Among these, NHEJ and HRR are the two major repair mechanisms for DSBs in eukaryotes, BER enzymes are major players for SSB repair (Dianov and Hubscher, 2013), and NER works for other bulk single-strand lesions. During these processes, various complexes of cellular proteins are recruited to DNA damage loci to activate DNA damage-responsive phosphatidylinositide 3 kinase (PI3K)-like Ser/Thr kinases, which consist of ATM, ATR, and DNA-dependent protein kinase catalytic subunit kinase (DNA-PKcs). For example, the heterotrimeric meiotic recombination 11 (Mre11)/Rad50/Nijmegen breakage syndrome protein 1 (NBS1) (MRN) complex (Carney *et al.*, 1998) and the Ku70/Ku80 complex (Cary *et al.*, 1997) are responsible for repairing DSBs. When cells experience SSBs, the Rad9-Hus1-Rad1 (9-1-1) complex is activated to facilitate recruitment of the replication protein A (RPA) and other factors. The functions of ATM and ATR (Fig. 1) will be addressed in detail below.

2.2 Function and regulation of ATM

ATM function and activation in the DDR depend on its phosphorylation. When cells encounter DNA damage signals, the MRN complex provides the platform for inactivated ATM to be phosphorylated (Lee and Paull, 2004). Several other cellular factors are also necessary to activate ATM directly or indirectly, such as Tat interactive protein 60 (Tip60) (Sun *et al.*, 2005), poly adenosine diphosphate (ADP)-ribose polymerase (PARP) (Aguilar-Quesada *et al.*, 2007), and phosphatase and tensin homolog (PTEN) (Zhang R. *et al.*, 2016). A number of factors can attenuate ATM phosphorylation including the serine/

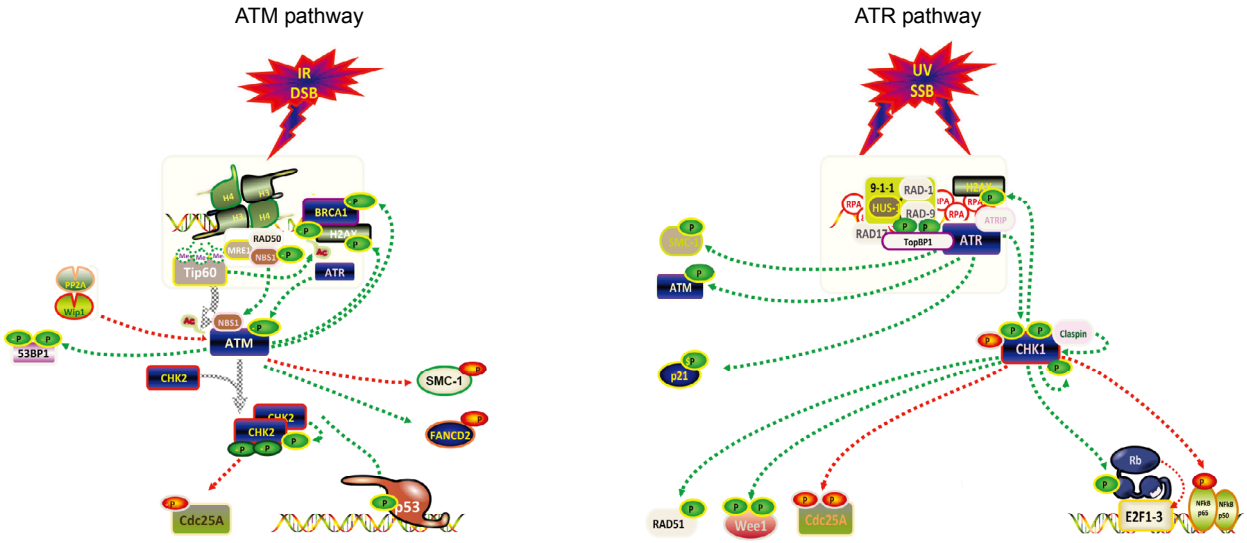

Fig. 1 Signaling pathways of ATM and ATR

The DNA damage response is activated by ATM, ATR, and DNA-PKcs. All three play central roles in DDR. The ATM-CHK2 and ATR-CHK1 signaling pathways activate the HRR. The ATM and ATR pathways can be activated respectively by DSBs and SSBs. ATM activation can be regulated by Tip60, MRN complex, ATR, and PP2A as well as Wip1. The activated ATM can further trigger the activation of CHK2, SMC-1, FANCD2, BRCA1, as well as H2AX. In addition, the activated CHK2 can phosphorylate Cdc25A and p53. The ATR pathway can be activated by ATRIP, TopBP1, claspin, and 9-1-1 complex. The activation of ATR leads to phosphorylation of various downstream targets such as CHK1, SMC-1, ATM, and p21. Furthermore, CHK1 can facilitate phosphorylation of Wee1, RAD51, Cdc25A, p65, and Rb

threonine protein phosphatases such as PP2A, Wip1, and PP5 (Ali *et al.*, 2004; Goodarzi *et al.*, 2004; Shreeram *et al.*, 2006). The activated ATM kinase phosphorylates Kruppel-associated box (KRAB)-associated protein-1 (White *et al.*, 2006), releases this substrate from the DNA lesion, and facilitates the recruitment of MRE11 and C-terminal binding protein (CtBP)-interacting protein (Ziv *et al.*, 2006; Goodarzi *et al.*, 2008). In addition, ATM activation leads to the formation of RAD51 nucleofilaments and the formation of RAD51/γ-H2AX foci (Bakr *et al.*, 2015). The histone variant H2AX, which spreads to sites and DNA breaks, can be also phosphorylated by ATM (Burma *et al.*, 2001).

ATM activation is important for the regulation of cell cycle checkpoints and downstream pathways. For the G1/S checkpoint, ATM triggers a p53-independent checkpoint kinase 2 (CHK2)/Cdc25A arm (Falck *et al.*, 2001) and an MDM2/p53 arm (Maya *et al.*, 2001). *S*-phase checkpoint control depends on the activation of NBS1, breast cancer type 1 susceptibility protein (BRCA1) and Fanconi anemia group D2 protein (FANCD2) (Gatei *et al.*, 2001; D'Amours and Jackson, 2002; Taniguchi *et al.*, 2002). ATM activation inhibits Cdc25 phosphatase resulting in S/G2 arrest (Matsuoka *et al.*, 1998). G2/M arrest can be mediated by BRCA1 or p53 in a Cdc2- or Cdc25C-dependent manner. The downstream effector kinase CHK2 activation triggers Cdc25C phosphorylation causing a G2/M arrest (Zhou *et al.*, 2000). In addition, ATM mediates p53 phosphorylation and stabilization to regulate cyclin-dependent kinase 2 (CDK2)/cyclin E-dependent G1 cell cycle arrest (Canman *et al.*, 1994; Banin *et al.*, 1998). Many substrates, including γ-H2AX (Fernandez-Capetillo *et al.*, 2004), the cohesin factor structural maintenance chromosome-1 (SMC-1) (Kitagawa *et al.*, 2004), and CHK2 (Bouwman and Jonkers, 2012), are recruited to the sites of damage. As a consequence, CHK2 is activated, which then phosphorylates additional substrates such as BRCA1 tumor suppressor (Cortez *et al.*, 1999), p53 tumor suppressor (Chen *et al.*, 2005), and the Cdc25 family of phosphatases (Blasina *et al.*, 1999).

2.3 Function and regulation of ATR

In parallel to ATM signaling, ATR signaling is critical to HRR in response to SSBs. ATR is known to be important to cell survival and its inactivation in mice by disruption of the kinase domain results in early embryonic lethality (de Klein *et al.*, 2000). Furthermore, a splicing mutation of ATR leads to Seckel syndrome (O'Driscoll *et al.*, 2003). In response

to DNA damage stimuli, long stretches of single strand DNA (ssDNA) are generated, which are coated with RPA (Coverley *et al.*, 1992). ATR is recruited to RPA-ssDNA complex and interacts with its canonical partners: ATR-interacting protein (ATRIP) (Zou and Elledge, 2003), claspin (Kumagai and Dunphy, 2003) and topoisomerase IIβ-binding protein 1 (TopBP1) (Kumagai *et al.*, 2006). Among these, TopBP1 interacts with the 9-1-1 complex, which is recruited to ssDNA lesions. ATR kinase activities can be regulated by several factors such as ATRIP (Zou and Elledge, 2003) and TopBP1 (Kumagai *et al.*, 2006). Once activated, ATR phosphorylates various downstream substrates including BRCA1 (Chen, 2000), MCM proteins (Cortez *et al.*, 2004), and checkpoint kinase 1 (CHK1) (Liu *et al.*, 2000). In turn, CHK1 phosphorylates Cdc25A (Falck *et al.*, 2002), Wee1 kinase (Lee *et al.*, 2001), and RAD51 (Sorensen *et al.*, 2005).

The ATR pathway can be activated not only by SSBs but also by DSBs. Recent studies have provided evidence that the ATR and ATM pathways are interlinked (Smith J. *et al.*, 2010). For example, ATM phosphorylation is necessary for a rapid activation of ATR when cells are exposed to DSBs (Byun *et al.*, 2005; Myers and Cortez, 2006). ATR activation by radiation-stimulated DSBs shares a common pattern of induction of an S/G2 phase arrest with ATM signaling (Jazayeri *et al.*, 2006; Walker *et al.*, 2009). In addition, activation of ATR signaling depends on the MRN complex that is also necessary for ATM signaling (Yarden *et al.*, 2002; Myers and Cortez, 2006). Both the ATM and ATR pathways can be manipulated by various viruses, such as Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), and HPV (McFadden and Luftig, 2013; Hollingworth and Grand, 2015). The regulation of the ATM/ATR pathways by HPV will be discussed later.

3 Life cycle of HPVs

3.1 HPV life cycle

HPVs are the major etiological agents responsible for cervical cancer (Zur Hausen, 2002). In recent years HPVs have been shown also to be involved in many other genital cancers such as those of the vulva, vagina, anus, penis, and oral cavity. About nine types of HPVs are considered as high-risk types, including HPV16, HPV18, HPV31, and HPV45, that are the causative agents of most anogenital cancers. The low-risk types, including HPV6 and HPV11, can cause genital warts. The life cycle of HPVs is dependent on epithelial differentiation (Fig. 2). During infection, HPVs escape immune surveillance and can remain latent for decades. HPVs infect stratified squamous epithelia by entering the cells in the basal layer that becomes exposed following trauma or wounding (Hebner and Laimins, 2006; Doorbar *et al.*, 2012). The infected basal cell divides into a new basal cell and a daughter cell that migrates to the upper layers of the epithelium as it undergoes terminal differentiation. HPV episomes are replicated and equally distributed to the new basal cell and the daughter cell.

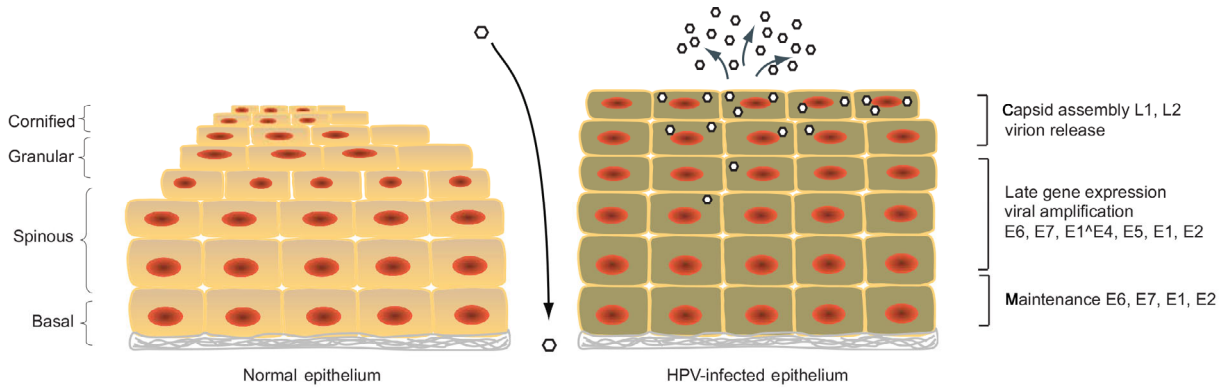

Fig. 2 Life cycle of human papillomaviruses

HPVs infect basal layer keratinocytes when the basal layer of stratified epithelia is exposed to the virus. On the left, a normal uninfected epithelium is shown for the regular differentiation. On the right, the HPV-infected epithelium is shown with the progress of HPV viral proteins expression. After persisting infection, HPVs replicate with cellular chromosomes in basal cells. Upon the differentiation, more viral genes are observed in differentiated cells. The late gene expression and viral replication are activated, followed by virion assembly and release of newly synthesized virions from the top layers of epithelium

HPVs maintain low copy numbers of viral genomes (around 100 copies per cell) in undifferentiated cells. Upon differentiation, the viral copy number increases rapidly to levels of around 1000 copies per cell in a process referred to as amplification. This is followed by virion assembly and viral release from the upper layers of the epithelium (Longworth and Laimins, 2004).

3.2 HPV viral protein function

The genomes of HPVs are about 8 kb in size and encode multiple viral gene products, including E1, E2, E4, E5, E6, E7, as well as L1 and L2 (Hebner and Laimins, 2006). E1 and E2 are two genes that regulate initiation of HPV genome replication (Sedman and Stenlund, 1995; McBride, 2013), whereas E4 and E5 regulate late viral functions (Dimaio and Petti, 2013). E6 and E7 are necessary for HPV genome maintenance and amplification, and act as two oncogenes to alter the host environment to be advantageous for viral replication (Thomas *et al.*, 1999; Munger and Howley, 2002; Wise-Draper and Wells, 2008; Wallace and Galloway, 2015). L1 and L2 are the two capsid proteins synthesized following productive replication (Hebner and Laimins, 2006; Thomas *et al.*, 2008).

HPV viral proteins function cooperatively to regulate the HPV life cycle. The E1 protein acts as a DNA helicase/ATPase to facilitate DNA unwinding and recruits host DNA polymerases to viral origins (Hughes and Romanos, 1993; Conger *et al.*, 1999). E2 has DNA-binding activities and is important for DNA segregation in mitotic cells (Oliveira *et al.*, 2006; Poddar *et al.*, 2009). Bromodomain-containing protein 4 (Brd4) has been implicated in this E2 function, and the interaction between Brd4 and E2 is also required for E2-dependent transcriptional regulation (McPhillips *et al.*, 2006; Wu *et al.*, 2006). In addition, E2 regulates expressions of E6, E7, E1, as well as E2 itself via controlling transcription of the early viral promoter (Steger and Corbach, 1997). E8^E2C is a truncated form of E2 that inhibits early gene expression and viral replication (Stubenrauch *et al.*, 2000). E1 and E2 work cooperatively in the initiation of viral replication (Frattini and Laimins, 1994; Sedman and Stenlund, 1995). E6 and E7 promote genome maintenance and viral replication (Cheng *et al.*, 1995; Thomas *et al.*, 1999) in addition to their roles in cell transformation and immortalization. An HPV31 genome containing an E6 or E7 mutation is not able to be maintained stably as an episome (Thomas *et al.*, 1999). The high-risk E6 binds to the cellular E3 ubiquitin ligase E6-associated protein (E6AP) to degrade p53 (Scheffner *et al.*, 1990; 1993; Huibregtse *et al.*, 1991) and to inhibit p53 function by blocking acetylation (Hebner *et al.*, 2007) in a p300-dependent manner (Patel *et al.*, 1999). The E7 protein binds to pRb to facilitate the regulation of cell cycle events by E2F family members (Dyson *et al.*, 1989; Munger *et al.*, 1989; Longworth *et al.*, 2005). E5 has been shown to be involved in cell motility, adhesion, and proliferation (Kivi *et al.*, 2008; Liao *et al.*, 2013). L1 and L2 capsid proteins are responsible for viral chromatin packaging and virion assembly (Nelson *et al.*, 2002; Darshan *et al.*, 2004). The lack of viral DNA polymerases and other necessary factors leads HPVs to rely on host factors to accomplish genome amplification.

4 Regulation of HPV viral replication

4.1 Classification of regulators for HPV viral replication

HPV viral replication is dependent on epithelial differentiation, and is regulated by viral factors, such as E1 and E2 (Kadaja *et al.*, 2009), and host factors. Because HPVs do not encode their own DNA polymerases and other factors, their replication is largely dependent on host factors such as transcriptional factors, microRNAs (miRs), kinases, apoptotic caspases, epigenetic enzymes, and DNA damage signaling (Moody and Laimins, 2010; Kajitani *et al.*, 2012; Hong and Laimins, 2013b). Before describing the interaction between the HPV life cycle and the DDR, I will provide a general description of what is known about the cellular factors involved in HPV viral replication, though the actual process of amplification is still not clear. The regulation of HPV viral replication by the DDR will be then discussed in detail in the following section.

4.2 Cellular enzymes

Several of the host factors that are important for HPV viral replication have been identified as cellular enzymes associated with the DDR. For example, the ubiquitin-specific protease 1 (USP1)-associated factor 1 (UAF1)-USP deubiquitinase complex, which is

suggested to be associated with the DDR (Chen *et al.*, 2011), can be recruited by E1 to facilitate HPV DNA replication (Lehoux *et al.*, 2014). The activated CDK2 phosphorylates NBS1 (Wohlbold *et al.*, 2012) and mediates HPV genome maintenance (Fradet-Turcotte *et al.*, 2010). The activity of caspase-3 is required for HPV genome replication (Moody *et al.*, 2007), and caspase-3-dependent apoptosis can be inhibited by ATR/CHK1 (Myers *et al.*, 2009). Activation of the nuclear factor-κB (NF-κB) pathway has been implicated in HPV genome amplification (Nakahara *et al.*, 2015; Satsuka *et al.*, 2015) and can be induced by DNA damage (Janssens and Tschopp, 2006). The deregulation of these factors suggests that HPV induces the DDR while suppressing cellular apoptotic events. Furthermore, binding of histone deacetylases (HDAC) to E7 contributes to E7-facilitated HPV genome amplification (Longworth *et al.*, 2005) and HDACs have been reported to function in the DDR (Miller *et al.*, 2010; Thurn *et al.*, 2013). The deacetylase sirtuin 1 facilitates HPV DNA replication, partly by modulating histone acetylation (Langsfeld *et al.*, 2015). In addition, repression of Brd4, which insulates chromatin from DNA damage signaling (Floyd *et al.*, 2013), deregulates E2-dependent HPV oncogene expression (Smith J.A. *et al.*, 2010). The association of these factors with HPV genomes further indicates that the DDR is involved in HPV viral replication.

4.3 Transcription factors

Cellular transcription factors also play a role in HPV viral replication. Some, including YY-1 (Ai *et al.*, 2000), TATA-binding protein (TBP) (Hartley and Alexander, 2002), activator protein 1 (AP-1) (Offord and Beard, 1990), Oct-1 (O'Connor and Bernard, 1995), and Sp1 (Stunkel and Bernard, 1999), act on the HPV early promoters located upstream of the E6 open reading frame (ORF). Others, such as CCAAT/enhancer binding protein β (C/EBPβ) isoforms, liver-enriched inhibitory protein (LIP), and liver-enriched transcriptional activator protein (LAP) (Gunasekharan *et al.*, 2012), act on the late promoter. Several of these transcription factors have been shown to be related to the DDR. For example, YY-1 is essential in homologous recombination-based DNA repair (Wu *et al.*, 2007). Downregulation of the subunit of TBP is responsible for DNA damage-induced repression of RNA polymerase III transcription (Ghavidel and Schultz, 2001). Activation of Oct-1 can be induced by DNA damage (Zhao *et al.*, 2000). The phosphorylated Sp1 colocalizes with γ-H2AX and depletion of Sp1 inhibits the repair of DSBs (Beishline *et al.*, 2012). In addition, members of the STAT family can be differently regulated by HPVs to facilitate viral replication. Inhibition of STAT-1 by E6 and E7 is necessary for HPV genome amplification (Hong *et al.*, 2011). In contrast, STAT-5 is activated by E7 and this activation is important for HPV genome amplification (Hong and Laimins, 2013a). Another transcription factor, Kruppel-like factor 13, can regulate STAT-5 expression, and is important for the differentiation-dependent HPV life cycle (Zhang W. *et al.*, 2016). The relationship between STAT-5 and the DDR will be discussed later.

4.4 MicroRNAs

miRs are among other cellular factors involved in HPV viral replication. The miRs are noncoding regulatory RNAs, 18–25 nucleotides in size. They post-transcriptionally regulate mRNA stability and translation and have been reported to be associated with the DDR (Wan *et al.*, 2011; Wang and Taniguchi, 2013). miRs are also associated with cervical cancer (Pedroza-Torres *et al.*, 2014) and can be considered as biomarkers for high-risk HPV infection (Wang *et al.*, 2014). HPV E7 down-regulates miR-203 and this suppression is required for HPV genome amplification through regulation of p63 (Melar-New and Laimins, 2010) and ATM DDR (Mighty and Laimins, 2011). miR-145, which is also suppressed by E7 and targets E1 ORFs, is important for HPV genome amplification (Gunasekharan and Laimins, 2013). Ectopic expression of miR-125b suppresses HPV gene expression (Nuovo *et al.*, 2010) possibly due to the sequence homology between HPV16 L2 and miR-125b. The role of these HPV-related miRs in the DDR is still not clear.

5 HPV and DDR

5.1 HPV regulates the DDR

Upon DNA damage, many host repair factors are recruited to the damage loci to repair single or double strand breaks. HPVs hijack this repair machinery, by

both inhibiting and activating the DDR, to replicate viral genes (Hong and Laimins, 2013b; Wallace and Galloway, 2014; 2015; McKinney *et al.*, 2015). For example, HPV oncogenes have been suggested to abrogate radiation-induced DDRs (Song *et al.*, 1998), and recent studies support the idea that HPVs regulate the DDR to mediate their life cycle. HPV E7 activates the FA repair pathway, enhances FANCD2 foci, and recruits FANCD2 and BRCA2 to chromatin (Spardy *et al.*, 2007). Both E6 and E7 interact with BRCA1 to inhibit its transcriptional regulation (Zhang *et al.*, 2005). HPV E6 disrupts p53 signaling (Thomas and Chiang, 2005) and interferes SSBs through interactions with XRCC1 and O^6-methylguanine-DNA methyltransferase (Iftner *et al.*, 2002; Srivenugopal and Ali-Osman, 2002).

Besides regulation of the DDR proteins mentioned above, HPVs are capable of manipulating host genomic destabilization. E6 and E7 can induce DNA damage independently by causing host chromosome instability (Duensing and Munger, 2002), and collaboratively by uncoupling centrosome duplication from the cell division cycle (Duensing *et al.*, 2000). Delocalization of the microtubule motor dynein by E7 results in failed chromosome alignment (Nguyen *et al.*, 2008). The expression of E7 results in polyploidy by inducing HPV rereplication in response to DNA damage (Fan *et al.*, 2013). In addition, E1 and E2 act as recruiters to facilitate colocalization of the DDR proteins with the HPV replication complex, which will be addressed below.

5.2 HPV regulates ATM and ATR pathways

The two major arms of the DDR are the ATM/CHK2 and ATR/CHK1 pathways. Little is known about how HPVs employ these two arms for the viral life cycle. ATM activation can be induced by high-risk HPV E1 and E7 proteins. For example, HPV18 E1 could cause DSBs and lead to the induction of an ATM-dependent signaling cascade (Reinson *et al.*, 2013). The HPV31 E7 oncoprotein binds to ATM and induces phosphorylation of ATM and CHK2 (Moody and Laimins, 2009). Similarly, HPV18 E7 induces elevated expression of phosphorylated ATM, as well as CHK2 and c-Jun N-terminal kinases (JNKs) (Banerjee *et al.*, 2011). The activated ATM and CHK2 are recruited to the DNA repair centers that are colocalized with the HPV integrated replication sites (Kadaja *et al.*, 2009), suggesting a critical role of ATM signaling in recruitment of HPV DNA to the DNA repair centers to start viral DNA synthesis.

Less is known about the effect of the viral proteins on ATR activity. Several contradictory results have been reported by different groups. An elevation of ATR protein levels was indicated in HPV16 E7-expressing cells (Spardy *et al.*, 2008), whereas other studies showed that HPV16 E7 attenuates CHK1 phosphorylation by increasing claspin turnover (Spardy *et al.*, 2009). Activation of the ATR pathway is induced by HPV18 E1 and E2, but not E6 or E7 (Reinson *et al.*, 2013). However, recent studies have shown that HPV31 E7 increases ATR phosphorylation as well as CHK1 phosphorylation (Hong *et al.*, 2015b). The levels of phosphorylated CHK1 are also enhanced and sustained in HPV16 E6-expressing fibroblasts (Chen *et al.*, 2009). The complexity of ATR regulation by high-risk HPV proteins indicates that differences between HPV species might lead to different modulation of ATR activation and that HPV proteins employ different mechanisms to regulate ATR and ATM.

Unlike high-risk α HPV types, β HPV E6 reduces ATM protein levels (Wallace *et al.*, 2013) and abrogates ATR activities (Wallace *et al.*, 2012). The reduction of ATR protein levels can be explained by the degradation of p300 (Wallace *et al.*, 2012), which is regulated by protein kinase B (PKB/AKT) (Howie *et al.*, 2011). Furthermore, β HPV E6 inhibits the stability of p53 (Wallace *et al.*, 2014) and attenuates BRCA1 and BRCA2 expression as well as foci formation (Wallace *et al.*, 2015). The suppressive effect of β E6 on ATM/ATR signaling may reflect an increased cellular tolerance of DNA lesions and a reduced induction of apoptosis by the DDR. It is not known how this regulation contributes to β HPV genome amplification.

E1 and E2, instead of modulating the phosphorylation of factors of the ATM/ATR pathway, are parts of the viral replication complex that colocalize with these factors (Kadaja *et al.*, 2009). Several cellular replication factors colocalize with HPV18 E1 in HeLa cells, including RPA, proliferating cell nuclear antigen (PCNA), and death-associated protein (DAXX). HPV18 E1 also recruits the MRN and Ku70/Ku80 complexes to the viral replication complex, and induces ATM/CHK2 activation. The same study provided

some evidence that E1 is colocalized with ATRIP and CHK1. Another set of DDR proteins, including γ-H2AX and 53BP1, colocalizes with the HPV DNA foci (Gillespie *et al.*, 2012). It has been suggested that the function of E2 is to facilitate the translocation of the complex of E1 and the associated DDR proteins to the nuclear foci (Sakakibara *et al.*, 2011). In addition, Boner *et al.* (2002) showed that HPV16 E2 interacts with TopBP1, and that this interaction enhances the ability of E2 to activate transcription and replication. All these findings suggest that interactions of the DDR proteins and E1/E2 play an important role in the aggregation of the HPV viral replication complex and DNA damage repair factors in the nuclear foci.

5.3 ATM and ATR DDR are necessary for HPV viral replication

The fact that many DDR proteins are deregulated by HPVs suggests that the DDR plays a significant role in HPV genome amplification. This is supported by the finding that activation of the ATM pathway is necessary for HPV genome amplification (Moody and Laimins, 2009). The same study also showed that inhibition of ATM activities has no effect on HPV genome maintenance. NBS1, as one component of the MRN complex that facilitates ATM activation, is also required for HPV genome amplification (Anacker *et al.*, 2014). Consistently, BRCA1, as a downstream target of ATM, is important for HPV genome amplification (Chappell *et al.*, 2016). Another downstream target, SMC-1, is activated by HPV and is required for HPV genome amplification (Mehta *et al.*, 2015), whereas loss of FANCD2 stimulates HPV replication (Hoskins *et al.*, 2012). In addition, RAD51 plays essential roles in the DDR and binds to HPV31 genomes. Depletion of RAD51 or inhibition of RAD51's recombinase activity abolishes HPV viral replication upon differentiation (Chappell *et al.*, 2016). HPV's association with Brd4 leads to an increase in the rate of asynchronous DNA replication (Jang *et al.*, 2014).

Compared to the ATM pathway, the role of ATR signaling for HPV replication is less well known. HPV18 transient replication induces an accumulation of ATR signaling, indicating a role of ATR in the initiation of HPV18 replication (Reinson *et al.*, 2013). Recent studies have shown that inhibition of ATR activities reduces HPV genome amplification, and that inhibition of CHK1 activities suppresses HPV genome amplification (Hong *et al.*, 2015b). Edwards *et al.* (2013) also showed that inhibition of CHK1 significantly reduces HPV episome levels in undifferentiated cells. In addition, knockdown of TopBP1, which is upstream of the ATR activation, suppresses HPV viral replication (Hong *et al.*, 2015b). The interaction between TopBP1 and E2 also contributes to HPV genome amplification (Donaldson *et al.*, 2012). Taken together, both ATM signaling and the ATR pathway are important for HPV viral replication.

5.4 STAT-5 activation promotes both ATM and ATR signaling for HPV viral replication

Although there is mounting evidence that the DDR is important for HPV genome amplification, less is known about how HPV regulates it to accomplish its life cycle. Recent studies investigated the relationships between HPVs and the immune response, and found that HPVs might utilize immune factors to promote the DDR by deregulation of the STAT family that contains important regulators of the innate immune response (Beglin *et al.*, 2009; Stanley, 2012; Hong and Laimins, 2013b).

STAT signaling is part of the interferon (IFN) pathway. Canonically, IFN-α or IFN-β binds to a heterodimeric transmembrane receptor termed IFN ax-receptor (IFNAR) (Abbas *et al*., 2014) and activates the receptor-associated Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2), resulting in the phosphorylation of inactive STAT proteins translocating from the cytoplasm to the nucleus and the induction of hundreds of genes that act to block viral propagation. The STAT family consists of STAT-1, -2, -3, -4, -5, and -6. Upon phosphorylation, STAT-1 forms a complex referred to as IFN-stimulated gene factor (ISGF3) along with STAT-2 and IFN regulatory factor (IRF)-9. The ISGF3 complex binds to the IFN stimulated elements (ISRE) located in promoter regions of many IFN-stimulated genes (ISGs) to induce their expressions. Similarly, unphosphorylated STAT-5 becomes activated following binding of cytokines to the cytokine receptors resulting in the formation of either homo- or heterodimers between its two isoforms STAT-5α and STAT-5β, and translocation from the cytoplasm to the nucleus (Ferbeyre and Moriggl, 2011). STAT-1 can induce many ISGs such as IFN-inducible double-stranded RNA-dependent

protein kinase (PKR) and IFN-induced protein with tetratricopeptide repeats (IFIT) (Diamond and Farzan, 2013), while STAT-5 activates a different set of downstream genes (Doan *et al*., 2008). STAT-5 activities are important for the development and survival of lymphocytes (Heltemes-Harris and Farrar, 2012), as well as epithelial cells (Groner, 2002).

Evidence suggests that the STAT proteins are associated with the DDR. For example, STAT-1 is suggested to confer resistance to DNA damage (Cheon *et al*., 2013). STAT-3 has been shown to disrupt ATR/CHK1 signaling (Koganti *et al*., 2014) and phosphorylation of STAT-3 requires ATM activation (Zhang *et al*., 2003). STAT-5 shares 50% homology with STAT-1. Knockout mice lacking STAT-5 exhibit a perinatal lethal phenotype (Cui *et al*., 2004) and severely impaired lymphoid development (Yao *et al*., 2006). Over-expression of STAT-5 promotes the DDR and is associated with CHK2 activity (Eilon and Barash, 2011). This suggests that HPV might regulate the STAT proteins to promote the DDR.

Before discussing the relationship between the STAT proteins and the DDR, I will discuss the expression of the STAT family in HPV-positive cells. The Laimins group has shown that HPV specifically suppresses the expression of STAT-1, but not STAT-2 (Hong *et al*., 2011) or STAT-3 (unpublished). In contrast, HPV induces the constitutive activation of STAT-5 while only minimally affecting total levels (Hong and Laimins, 2013a). HPVs can also deregulate STAT expression by controlling the IRF transcription factors and synthesis of IFNs. For example, IRF-1 expression can be downregulated by HPV16 E7 (Park *et al*., 2000) and HPV38 E6E7 (Cordano *et al*., 2008). HPV16 E6 binds to IRF-3 to inhibit its transcriptional activity (Ronco *et al*., 1998). Consequently, IRF deregulation by HPV proteins leads to a reduced expression of IFN-α (Chang and Laimins, 2000), IFN-β (Ronco *et al*., 1998; Park *et al*., 2000), and IFN-κ (Rincon-Orozco *et al*., 2009). Among these, IFN-β has been shown to be associated with the DDR (Moiseeva *et al*., 2006; Cheon *et al*., 2013).

Hong and Laimins (2013a) have shown that inhibition of STAT-5 phosphorylation suppresses HPV genome amplification and late gene expression upon epithelial differentiation. This STAT-5-dependent regulation can be explained by two DDR mechanisms: the ATM (Hong and Laimins, 2013a) and the ATR pathways (Hong *et al*., 2015b) (Fig. 3). Inhibition of STAT-5 suppresses the phosphorylation of ATM, CHK2, ATR, CHK1, and BRCA1, as well as the level of RAD51, but not BRCA2 or SMC-1. These findings suggest that the DDR crosslinks with the immune response and both responses could be important for HPV viral replication.

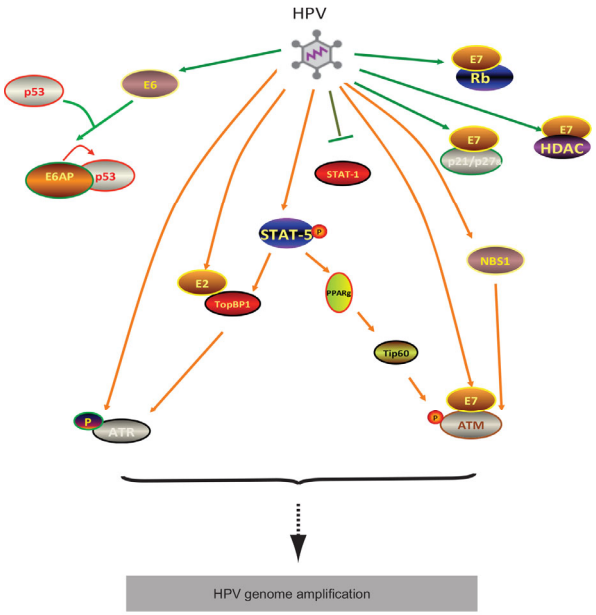

Fig. 3 STAT-5-dependent activation of ATM and ATR pathways, required for HPV genome amplification
High-risk HPV activates STAT-5 to mediate TopBP1 transcriptionally to promote ATR pathway. Meanwhile, STAT-5 does not directly regulate Tip60; instead, it partially work through PPARg to manipulate Tip60 activation which consequently facilitates ATM activation. HPV E7 oncogene is responsible for STAT-5 activation as well as interaction with other factors such as Rb, ATM, NBS1, HDAC, and p21. E6 gene may collaborate with other viral proteins to act on Tip60 in addition to its role in p53 degradation. E2 is capable of interacting with TopBP1 to mediate HPV initial replication

As a transcription factor, STAT-5 does not directly mediate the level of ATM or ATR. Instead, it deregulates the acetyltransferase Tip60 (Hong *et al*., 2015a) or TopBP1 (Hong *et al*., 2015b) to promote the activation of ATM or ATR signaling. Tip60 knockdown blocks ATM activation and HPV genome amplification upon differentiation. Both p53 and histone H2AX, the downstream targets of Tip60, may also play a role in the DDR in HPV-positive cells. Inhibition of STAT-5 activation blocks Tip60 activation and this regulation might be mediated by the

kinase glycogen synthase kinase 3β (GSK3β). Consistently, GSK3β inhibition also leads to reduced levels of viral episomes and impaired genome amplification.

STAT-5 regulates transcription of the TopBP1 gene to mediate ATR activation in HPV-positive cells and knockdown of TopBP1 blocks HPV genome amplification (Hong *et al.*, 2015b). Knockdown of TopBP1 moderately increases short-term replication of transiently transfected HPV31 plasmids and has a modest effect on stable maintenance of HPV31 episomes (Kanginakudru *et al.*, 2015). Hong *et al.* (2015b) identified a critical role for TopBP1 in the differentiation-dependent late phase of the viral life cycle. TopBP1 is also recruited to viral genomes by forming complexes with the HPV E2 protein. The failure of E2 to bind TopBP1 results in a reduced replication ability, indicating that it is a positive regulator of viral replication (Donaldson *et al.*, 2012). TopBP1 also helps to load replication factors onto origins (Gauson *et al.*, 2015) and acts as a transcriptional regulator (Liu *et al.*, 2003), but it is unclear if these functions are important for HPV genome amplification.

6 Perspectives

The complexity of the role of the DDR in the viral life cycle has been a recent focus of research. In the HPV field, although there have been some studies demonstrating the necessary roles of ATM or ATR signaling in HPV viral replication, more effort should be placed on the roles of the DDR factors in the HPV life cycle. What are the substrates for ATM or ATR that contribute to the HPV life cycle? What other DNA damage factors are important in HPV viral replication? Are DNA damage repair foci the same as HPV replication centers? An additional question raised here is whether the DDR is important for the development of cervical cancer. Moreover, I presented evidence that the immune regulator STAT-5 participates in activation of the ATM or ATR pathway to facilitate HPV genome amplification, suggesting that the interaction between the innate immune response and the DNA damage pathway needs to be dissected in detail. The role of other members of STATs, such as STAT-3, in DNA damage regulation and HPV genome amplification is still not clear. Further, is the DDR able to mediate the innate immune response as a feedback loop for HPV persistent infection? Resolving these questions will improve our understanding of the replication mechanisms of HPVs and provide insight for developing new therapeutic targets against HPV-related diseases.

Compliance with ethics guidelines

Shi-yuan HONG declares that he has no conflict of interest.

This article does not contain any studies with human or animal subjects performed by the author.

References

Abbas, A.K., Lichtman, A.H., Pillai, S., 2014. Cellular and Molecular Immunology. Elsevier Saunders, Philadelphia, PA.

Aguilar-Quesada, R., Munoz-Gamez, J.A., Martin-Oliva, D., *et al.*, 2007. Interaction between ATM and PARP-1 in response to DNA damage and sensitization of ATM deficient cells through PARP inhibition. *BMC Mol. Biol.*, **8**:29. http://dx.doi.org/10.1186/1471-2199-8-29

Ai, W., Narahari, J., Roman, A., 2000. Yin yang 1 negatively regulates the differentiation-specific E1 promoter of human papillomavirus type 6. *J. Virol*., **74**(11):5198-5205. http://dx.doi.org/10.1128/JVI.74.11.5198-5205.2000

Ali, A., Zhang, J., Bao, S., *et al.*, 2004. Requirement of protein phosphatase 5 in DNA-damage-induced ATM activation. *Genes Dev*., **18**(3):249-254. http://dx.doi.org/10.1101/gad.1176004

Anacker, D.C., Gautam, D., Gillespie, K.A., *et al.*, 2014. Productive replication of human papillomavirus 31 requires DNA repair factor NBS1. *J. Virol*., **88**(15): 8528-8544. http://dx.doi.org/10.1128/JVI.00517-14

Atamna, H., Cheung, I., Ames, B.N., 2000. A method for detecting abasic sites in living cells: age-dependent changes in base excision repair. *PNAS*, **97**(2):686-691. http://dx.doi.org/10.1073/pnas.97.2.686

Bakr, A., Oing, C., Kocher, S., *et al.*, 2015. Involvement of ATM in homologous recombination after end resection and RAD51 nucleofilament formation. *Nucleic Acids Res*., **43**(6):3154-3166. http://dx.doi.org/10.1093/nar/gkv160

Banerjee, N.S., Wang, H.K., Broker, T.R., *et al.*, 2011. Human papillomavirus (HPV) E7 induces prolonged G2 following S phase reentry in differentiated human keratinocytes. *J. Biol. Chem*., **286**(17):15473-15482. http://dx.doi.org/10.1074/jbc.M110.197574

Banin, S., Moyal, L., Shieh, S., *et al.*, 1998. Enhanced phosphorylation of p53 by ATM in response to DNA damage. *Science*, **281**(5383):1674-1677. http://dx.doi.org/10.1126/science.281.5383.1674

Beglin, M., Melar-New, M., Laimins, L., 2009. Human

papillomaviruses and the interferon response. *J. Interferon Cytokine Res*., **29**(9):629-635. http://dx.doi.org/10.1089/jir.2009.0075

Beishline, K., Kelly, C.M., Olofsson, B.A., *et al.*, 2012. Sp1 facilitates DNA double-strand break repair through a nontranscriptional mechanism. *Mol. Cell. Biol*., **32**(18): 3790-3799. http://dx.doi.org/10.1128/MCB.00049-12

Blasina, A., de Weyer, I.V., Laus, M.C., *et al.*, 1999. A human homologue of the checkpoint kinase Cds1 directly inhibits Cdc25 phosphatase. *Curr. Biol*., **9**(1):1-10. http://dx.doi.org/10.1016/S0960-9822(99)80041-4

Boner, W., Taylor, E.R., Tsirimonaki, E., *et al.*, 2002. A functional interaction between the human papillomavirus 16 transcription/replication factor E2 and the DNA damage response protein TopBP1. *J. Biol. Chem*., **277**(25): 22297-22303. http://dx.doi.org/10.1074/jbc.M202163200

Bouwman, P., Jonkers, J., 2012. The effects of deregulated DNA damage signalling on cancer chemotherapy response and resistance. *Nat. Rev. Cancer*, **12**(9):587-598. http://dx.doi.org/10.1038/nrc3342

Burma, S., Chen, B.P., Murphy, M., *et al.*, 2001. ATM phosphorylates histone H2AX in response to DNA double-strand breaks. *J. Biol. Chem*., **276**(45):42462-42467. http://dx.doi.org/10.1074/jbc.C100466200

Byun, T.S., Pacek, M., Yee, M.C., *et al.*, 2005. Functional uncoupling of MCM helicase and DNA polymerase activities activates the ATR-dependent checkpoint. *Genes Dev*., **19**(9):1040-1052. http://dx.doi.org/10.1101/gad.1301205

Canman, C.E., Wolff, A.C., Chen, C.Y., *et al.*, 1994. The p53-dependent G1 cell cycle checkpoint pathway and ataxia-telangiectasia. *Cancer Res*., **54**(19):5054-5058.

Carney, J.P., Maser, R.S., Olivares, H., *et al.*, 1998. The hMre11/hRad50 protein complex and Nijmegen breakage syndrome: linkage of double-strand break repair to the cellular DNA damage response. *Cell*, **93**(3):477-486.

Cary, R.B., Peterson, S.R., Wang, J., *et al.*, 1997. DNA looping by Ku and the DNA-dependent protein kinase. *PNAS*, **94**(9):4267-4272. http://dx.doi.org/10.1073/pnas.94.9.4267

Chang, Y.E., Laimins, L.A., 2000. Microarray analysis identifies interferon-inducible genes and STAT-1 as major transcriptional targets of human papillomavirus type 31. *J. Virol*., **74**(9):4174-4182. http://dx.doi.org/10.1128/JVI.74.9.4174-4182.2000

Chappell, W.H., Gautam, D., Ok, S.T., *et al.*, 2016. Homologous recombination repair factors RAD51 and BRCA1 are necessary for productive replication of human papillomavirus 31. *J. Virol*., **90**(5):2639-2652. http://dx.doi.org/10.1128/JVI.02495-15

Chen, B., Simpson, D.A., Zhou, Y., *et al.*, 2009. Human papilloma virus type16 E6 deregulates CHK1 and sensitizes human fibroblasts to environmental carcinogens independently of its effect on p53. *Cell Cycle*, **8**(11): 1775-1787. http://dx.doi.org/10.4161/cc.8.11.8724

Chen, J., 2000. Ataxia telangiectasia-related protein is involved in the phosphorylation of BRCA1 following deoxyribonucleic acid damage. *Cancer Res*., **60**(18):5037-5039.

Chen, J., Dexheimer, T.S., Ai, Y., *et al.*, 2011. Selective and cell-active inhibitors of the USP1/UAF1 deubiquitinase complex reverse cisplatin resistance in non-small cell lung cancer cells. *Chem. Biol*., **18**(11):1390-1400. http://dx.doi.org/10.1016/j.chembiol.2011.08.014

Chen, L., Gilkes, D.M., Pan, Y., *et al.*, 2005. ATM and Chk2-dependent phosphorylation of mdmx contribute to p53 activation after DNA damage. *EMBO J*., **24**(19): 3411-3422. http://dx.doi.org/10.1038/sj.emboj.7600812

Cheng, S., Schmidt-Grimminger, D.C., Murant, T., *et al.*, 1995. Differentiation-dependent up-regulation of the human papillomavirus E7 gene reactivates cellular DNA replication in suprabasal differentiated keratinocytes. *Genes Dev*., **9**(19):2335-2349. http://dx.doi.org/10.1101/gad.9.19.2335

Cheon, H., Holvey-Bates, E.G., Schoggins, J.W., *et al.*, 2013. IFNβ-dependent increases in STAT1, STAT2, and IRF9 mediate resistance to viruses and DNA damage. *EMBO J*., **32**(20):2751-2763. http://dx.doi.org/10.1038/emboj.2013.203

Conger, K.L., Liu, J.S., Kuo, S.R., *et al.*, 1999. Human papillomavirus DNA replication. Interactions between the viral E1 protein and two subunits of human DNA polymerase α/PRIMASE. *J. Biol. Chem*., **274**(5):2696-2705. http://dx.doi.org/10.1074/jbc.274.5.2696

Cordano, P., Gillan, V., Bratlie, S., *et al.*, 2008. The E6E7 oncoproteins of cutaneous human papillomavirus type 38 interfere with the interferon pathway. *Virology*, **377**(2): 408-418. http://dx.doi.org/10.1016/j.virol.2008.04.036

Cortez, D., Wang, Y., Qin, J., *et al.*, 1999. Requirement of ATM-dependent phosphorylation of BRCA1 in the DNA damage response to double-strand breaks. *Science*, **286**(5442):1162-1166. http://dx.doi.org/10.1126/science.286.5442.1162

Cortez, D., Glick, G., Elledge, S.J., 2004. Minichromosome maintenance proteins are direct targets of the ATM and ATR checkpoint kinases. *PNAS*, **101**(27):10078-10083. http://dx.doi.org/10.1073/pnas.0403410101

Coverley, D., Kenny, M.K., Lane, D.P., *et al.*, 1992. A role for the human single-stranded DNA binding protein HSSB/RPA in an early stage of nucleotide excision repair. *Nucleic Acids Res*., **20**(15):3873-3880. http://dx.doi.org/10.1093/nar/20.15.3873

Cui, Y., Riedlinger, G., Miyoshi, K., *et al.*, 2004. Inactivation of STAT5 in mouse mammary epithelium during pregnancy reveals distinct functions in cell proliferation, survival, and differentiation. *Mol. Cell. Biol*., **24**(18): 8037-8047.

http://dx.doi.org/10.1128/MCB.24.18.8037-8047.2004

Curtin, N.J., 2012. DNA repair dysregulation from cancer driver to therapeutic target. *Nat. Rev. Cancer*, **12**(12): 801-817.
http://dx.doi.org/10.1038/nrc3399

D'Amours, D., Jackson, S.P., 2002. The MRE11 complex: at the crossroads of DNA repair and checkpoint signalling. *Nat. Rev. Mol. Cell Biol*., **3**(5):317-327.
http://dx.doi.org/10.1038/nrm805

Darshan, M.S., Lucchi, J., Harding, E., *et al.*, 2004. The L2 minor capsid protein of human papillomavirus type 16 interacts with a network of nuclear import receptors. *J. Virol*., **78**(22):12179-12188.
http://dx.doi.org/10.1128/JVI.78.22.12179-12188.2004

de Klein, A., Muijtjens, M., van Os, R., *et al.*, 2000. Targeted disruption of the cell-cycle checkpoint gene *ATR* leads to early embryonic lethality in mice. *Curr. Biol*., **10**(8): 479-482.
http://dx.doi.org/10.1016/S0960-9822(00)00447-4

Diamond, M.S., Farzan, M., 2013. The broad-spectrum antiviral functions of IFIT and IFITM proteins. *Nat. Rev. Immunol*., **13**(1):46-57.
http://dx.doi.org/10.1038/nri3344

Dianov, G.L., Hubscher, U., 2013. Mammalian base excision repair: the forgotten archangel. *Nucleic Acids Res*., **41**(6): 3483-3490.
http://dx.doi.org/10.1093/nar/gkt076

Dimaio, D., Petti, L.M., 2013. The E5 proteins. *Virology*, **445**(1-2):99-114.
http://dx.doi.org/10.1016/j.virol.2013.05.006

Doan, T., Melvold, R., Viselli, S., *et al*., 2008. Lippincott's Illustrated Reviews: Immunology. Wolters Kluwer Health/Lippincott Williams & Wilkins.

Donaldson, M.M., Mackintosh, L.J., Bodily, J.M., *et al.*, 2012. An interaction between human papillomavirus 16 E2 and TopBP1 is required for optimum viral DNA replication and episomal genome establishment. *J. Virol*., **86**(23): 12806-12815.
http://dx.doi.org/10.1128/JVI.01002-12

Doorbar, J., Quint, W., Banks, L., *et al.*, 2012. The biology and life-cycle of human papillomaviruses. *Vaccine*, **30**(Suppl. 5): F55-F70.
http://dx.doi.org/10.1016/j.vaccine.2012.06.083

Duensing, S., Munger, K., 2002. The human papillomavirus type 16 E6 and E7 oncoproteins independently induce numerical and structural chromosome instability. *Cancer Res*., **62**(23):7075-7082.

Duensing, S., Lee, L.Y., Duensing, A., *et al.*, 2000. The human papillomavirus type 16 E6 and E7 oncoproteins cooperate to induce mitotic defects and genomic instability by uncoupling centrosome duplication from the cell division cycle. *PNAS*, **97**(18):10002-10007.
http://dx.doi.org/10.1073/pnas.170093297

Dyson, N., Howley, P.M., Munger, K., *et al.*, 1989. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science*, **243**(4893):934-937.
http://dx.doi.org/10.1126/science.2537532

Edwards, T.G., Helmus, M.J., Koeller, K., *et al.*, 2013. Human papillomavirus episome stability is reduced by aphidicolin and controlled by DNA damage response pathways. *J. Virol*., **87**(7):3979-3989.
http://dx.doi.org/10.1128/JVI.03473-12

Eilon, T., Barash, I., 2011. Forced activation of Stat5 subjects mammary epithelial cells to DNA damage and preferential induction of the cellular response mechanism during proliferation. *J. Cell. Physiol*., **226**(3):616-626.
http://dx.doi.org/10.1002/jcp.22381

Falck, J., Mailand, N., Syljuasen, R.G., *et al.*, 2001. The ATM-Chk2-Cdc25A checkpoint pathway guards against radioresistant DNA synthesis. *Nature*, **410**(6830):842-847.
http://dx.doi.org/10.1038/35071124

Falck, J., Petrini, J.H., Williams, B.R., *et al.*, 2002. The DNA damage-dependent intra-S phase checkpoint is regulated by parallel pathways. *Nat. Genet*., **30**(3):290-294.
http://dx.doi.org/10.1038/ng845

Fan, X., Liu, Y., Heilman, S.A., *et al*., 2013. Human papillomavirus E7 induces rereplication in response to DNA damage. *J. Virol*., **87**(2):1200-1210.
http://dx.doi.org/10.1128/JVI.02038-12

Ferbeyre, G., Moriggl, R., 2011. The role of STAT5 transcription factors as tumor suppressors or oncogenes. *Biochim. Biophys. Acta*, **1815**(1):104-114.
http://dx.doi.org/10.1016/j.bbcan.2010.10.004

Fernandez-Capetillo, O., Lee, A., Nussenzweig, M., *et al.*, 2004. H2AX: the histone guardian of the genome. *DNA Repair (Amst.)*, **3**(8-9):959-967.
http://dx.doi.org/10.1016/j.dnarep.2004.03.024

Floyd, S.R., Pacold, M.E., Huang, Q., *et al.*, 2013. The bromodomain protein Brd4 insulates chromatin from DNA damage signalling. *Nature*, **498**(7453):246-250.
http://dx.doi.org/10.1038/nature12147

Fradet-Turcotte, A., Moody, C., Laimins, L.A., *et al*., 2010. Nuclear export of human papillomavirus type 31 E1 is regulated by Cdk2 phosphorylation and required for viral genome maintenance. *J. Virol*., **84**(22):11747-11760.
http://dx.doi.org/10.1128/JVI.01445-10

Frattini, M.G., Laimins, L.A., 1994. Binding of the human papillomavirus E1 origin-recognition protein is regulated through complex formation with the E2 enhancer-binding protein. *PNAS*, **91**(26):12398-12402.
http://dx.doi.org/10.1073/pnas.91.26.12398

Galloway, D.A., Laimins, L.A., 2015. Human papillomaviruses: shared and distinct pathways for pathogenesis. *Curr. Opin. Virol*., **14**:87-92.
http://dx.doi.org/10.1016/j.coviro.2015.09.001

Gatei, M., Zhou, B.B., Hobson, K., *et al.*, 2001. Ataxia telangiectasia mutated (ATM) kinase and ATM and Rad3 related kinase mediate phosphorylation of Brca1 at distinct and overlapping sites. In vivo assessment using phospho-specific antibodies. *J. Biol. Chem*., **276**(20): 17276-17280.
http://dx.doi.org/10.1074/jbc.M011681200

Gauson, E.J., Donaldson, M.M., Dornan, E.S., *et al.*, 2015. Evidence supporting a role for TopBP1 and Brd4 in the initiation but not continuation of human papillomavirus 16 E1/E2-mediated DNA replication. *J. Virol.*, **89**(9): 4980-4991.
http://dx.doi.org/10.1128/JVI.00335-15

Ghavidel, A., Schultz, M.C., 2001. TATA binding protein-associated CK2 transduces DNA damage signals to the RNA polymerase III transcriptional machinery. *Cell*, **106**(5):575-584.
http://dx.doi.org/10.1016/S0092-8674(01)00473-1

Gillespie, K.A., Mehta, K.P., Laimins, L.A., *et al.*, 2012. Human papillomaviruses recruit cellular DNA repair and homologous recombination factors to viral replication centers. *J. Virol.*, **86**(17):9520-9526.
http://dx.doi.org/10.1128/JVI.00247-12

Goodarzi, A.A., Jonnalagadda, J.C., Douglas, P., *et al.*, 2004. Autophosphorylation of ataxia-telangiectasia mutated is regulated by protein phosphatase 2A. *EMBO J.*, **23**(22): 4451-4461.
http://dx.doi.org/10.1038/sj.emboj.7600455

Goodarzi, A.A., Noon, A.T., Deckbar, D., *et al.*, 2008. ATM signaling facilitates repair of DNA double-strand breaks associated with heterochromatin. *Mol. Cell*, **31**(2):167-177.
http://dx.doi.org/10.1016/j.molcel.2008.05.017

Groner, B., 2002. Transcription factor regulation in mammary epithelial cells. *Domest. Anim. Endocrinol.*, **23**(1-2):25-32.
http://dx.doi.org/10.1016/S0739-7240(02)00142-X

Gunasekharan, V., Laimins, L.A., 2013. Human papillomaviruses modulate microRNA 145 expression to directly control genome amplification. *J. Virol.*, **87**(10):6037-6043.
http://dx.doi.org/10.1128/JVI.00153-13

Gunasekharan, V., Hache, G., Laimins, L., 2012. Differentiation-dependent changes in levels of C/EBPβ repressors and activators regulate human papillomavirus type 31 late gene expression. *J. Virol.*, **86**(9):5393-5398.
http://dx.doi.org/10.1128/JVI.07239-11

Hartley, K.A., Alexander, K.A., 2002. Human TATA binding protein inhibits human papillomavirus type 11 DNA replication by antagonizing E1-E2 protein complex formation on the viral origin of replication. *J. Virol.*, **76**(10): 5014-5023.
http://dx.doi.org/10.1128/JVI.76.10.5014-5023.2002

Hebner, C., Beglin, M., Laimins, L.A., 2007. Human papillomavirus E6 proteins mediate resistance to interferon-induced growth arrest through inhibition of p53 acetylation. *J. Virol.*, **81**(23):12740-12747.
http://dx.doi.org/10.1128/JVI.00987-07

Hebner, C.M., Laimins, L.A., 2006. Human papillomaviruses: basic mechanisms of pathogenesis and oncogenicity. *Rev. Med. Virol.*, **16**(2):83-97.
http://dx.doi.org/10.1002/rmv.488

Heltemes-Harris, L.M., Farrar, M.A., 2012. The role of STAT5 in lymphocyte development and transformation. *Curr. Opin. Immunol.*, **24**(2):146-152.
http://dx.doi.org/10.1016/j.coi.2012.01.015

Herrero, R., Hildesheim, A., Bratti, C., *et al.*, 2000. Population-based study of human papillomavirus infection and cervical neoplasia in rural Costa Rica. *J. Natl. Cancer Inst.*, **92**(6):464-474.
http://dx.doi.org/10.1093/jnci/92.6.464

Ho, G.Y., Burk, R.D., Klein, S., *et al.*, 1995. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J. Natl. Cancer Inst.*, **87**(18): 1365-1371.
http://dx.doi.org/10.1093/jnci/87.18.1365

Hollingworth, R., Grand, R.J., 2015. Modulation of DNA damage and repair pathways by human tumour viruses. *Viruses*, **7**(5):2542-2591.
http://dx.doi.org/10.3390/v7052542

Hong, S., Laimins, L.A., 2013a. The JAK-STAT transcriptional regulator, STAT-5, activates the ATM DNA damage pathway to induce HPV 31 genome amplification upon epithelial differentiation. *PLoS Pathog.*, **9**(4): e1003295.
http://dx.doi.org/10.1371/journal.ppat.1003295

Hong, S., Laimins, L.A., 2013b. Regulation of the life cycle of HPVs by differentiation and the DNA damage response. *Future Microbiol.*, **8**(12):1547-1557.
http://dx.doi.org/10.2217/fmb.13.127

Hong, S., Mehta, K.P., Laimins, L.A., 2011. Suppression of STAT-1 expression by human papillomaviruses is necessary for differentiation-dependent genome amplification and plasmid maintenance. *J. Virol.*, **85**(18):9486-9494.
http://dx.doi.org/10.1128/JVI.05007-11

Hong, S., Dutta, A., Laimins, L.A., 2015a. The acetyltransferase Tip60 is a critical regulator of the differentiation-dependent amplification of human papillomaviruses. *J. Virol.*, **89**(8):4668-4675.
http://dx.doi.org/10.1128/JVI.03455-14

Hong, S., Cheng, S., Iovane, A., *et al.*, 2015b. STAT-5 regulates transcription of the topoisomerase IIβ-binding protein 1 (TopBP1) gene to activate the ATR pathway and promote human papillomavirus replication. *MBio*, **6**(6): e02006-e02015.
http://dx.doi.org/10.1128/mBio.02006-15

Hoskins, E.E., Morreale, R.J., Werner, S.P., *et al.*, 2012. The fanconi anemia pathway limits human papillomavirus replication. *J. Virol.*, **86**(15):8131-8138.
http://dx.doi.org/10.1128/JVI.00408-12

Howie, H.L., Koop, J.I., Weese, J., *et al.*, 2011. Beta-HPV 5 and 8 E6 promote p300 degradation by blocking AKT/p300 association. *PLoS Pathog.*, **7**(8):e1002211.
http://dx.doi.org/10.1371/journal.ppat.1002211

Hughes, F.J., Romanos, M.A., 1993. E1 protein of human papillomavirus is a DNA helicase/ATPase. *Nucleic Acids Res.*, **21**(25):5817-5823.
http://dx.doi.org/10.1093/nar/21.25.5817

Huibregtse, J.M., Scheffner, M., Howley, P.M., 1991. A cellular protein mediates association of p53 with the E6 oncoprotein of human papillomavirus types 16 or 18. *EMBO J.*, **10**(13):4129-4135.

Iftner, T., Elbel, M., Schopp, B., *et al.*, 2002. Interference of papillomavirus E6 protein with single-strand break repair by interaction with XRCC1. *EMBO J.*, **21**(17):4741-4748. http://dx.doi.org/10.1093/emboj/cdf443

Jackson, S.P., Bartek, J., 2009. The DNA-damage response in human biology and disease. *Nature*, **461**(7267):1071-1078. http://dx.doi.org/10.1038/nature08467

Jang, M.K., Shen, K., McBride, A.A., 2014. Papillomavirus genomes associate with Brd4 to replicate at fragile sites in the host genome. *PLoS Pathog.*, **10**(5):e1004117. http://dx.doi.org/10.1371/journal.ppat.1004117

Janssens, S., Tschopp, J., 2006. Signals from within: the DNA-damage-induced NF-κB response. *Cell Death Differ.*, **13**(5):773-784. http://dx.doi.org/10.1038/sj.cdd.4401843

Jazayeri, A., Falck, J., Lukas, C., *et al.*, 2006. ATM- and cell cycle-dependent regulation of ATR in response to DNA double-strand breaks. *Nat. Cell Biol.*, **8**(1):37-45. http://dx.doi.org/10.1038/ncb1337

Kadaja, M., Isok-Paas, H., Laos, T., *et al.*, 2009. Mechanism of genomic instability in cells infected with the high-risk human papillomaviruses. *PLoS Pathog.*, **5**(4):e1000397. http://dx.doi.org/10.1371/journal.ppat.1000397

Kajitani, N., Satsuka, A., Kawate, A., *et al.*, 2012. Productive lifecycle of human papillomaviruses that depends upon squamous epithelial differentiation. *Front. Microbiol.*, **3**:152. http://dx.doi.org/10.3389/fmicb.2012.00152

Kanginakudru, S., Desmet, M., Thomas, Y., *et al.*, 2015. Levels of the E2 interacting protein TopBP1 modulate papillomavirus maintenance stage replication. *Virology*, **478**:135-142. http://dx.doi.org/10.1016/j.virol.2015.01.011

Kitagawa, R., Bakkenist, C.J., McKinnon, P.J., *et al.*, 2004. Phosphorylation of SMC1 is a critical downstream event in the ATM-NBS1-BRCA1 pathway. *Genes Dev.*, **18**(12):1423-1438. http://dx.doi.org/10.1101/gad.1200304

Kivi, N., Greco, D., Auvinen, P., *et al.*, 2008. Genes involved in cell adhesion, cell motility and mitogenic signaling are altered due to HPV 16 E5 protein expression. *Oncogene*, **27**(18):2532-2541. http://dx.doi.org/10.1038/sj.onc.1210916

Koganti, S., Hui-Yuen, J., McAllister, S., *et al.*, 2014. STAT3 interrupts ATR-Chk1 signaling to allow oncovirus-mediated cell proliferation. *PNAS*, **111**(13):4946-4951. http://dx.doi.org/10.1073/pnas.1400683111

Kumagai, A., Dunphy, W.G., 2003. Repeated phosphopeptide motifs in Claspin mediate the regulated binding of Chk1. *Nat. Cell Biol.*, **5**(2):161-165. http://dx.doi.org/10.1038/ncb921

Kumagai, A., Lee, J., Yoo, H.Y., *et al.*, 2006. TopBP1 activates the ATR-ATRIP complex. *Cell*, **124**(5):943-955. http://dx.doi.org/10.1016/j.cell.2005.12.041

Langsfeld, E.S., Bodily, J.M., Laimins, L.A., 2015. The deacetylase sirtuin 1 regulates human papillomavirus replication by modulating histone acetylation and recruitment of DNA damage factors NBS1 and RAD51 to viral genomes. *PLoS Pathog.*, **11**(9):e1005181. http://dx.doi.org/10.1371/journal.ppat.1005181

Lee, J., Kumagai, A., Dunphy, W.G., 2001. Positive regulation of Wee1 by Chk1 and 14-3-3 proteins. *Mol. Biol. Cell*, **12**(3):551-563. http://dx.doi.org/10.1091/mbc.12.3.551

Lee, J.H., Paull, T.T., 2004. Direct activation of the ATM protein kinase by the Mre11/Rad50/Nbs1 complex. *Science*, **304**(5667):93-96. http://dx.doi.org/10.1126/science.1091496

Lehoux, M., Gagnon, D., Archambault, J., 2014. E1-mediated recruitment of a UAF1-USP deubiquitinase complex facilitates human papillomavirus DNA replication. *J. Virol.*, **88**(15):8545-8555. http://dx.doi.org/10.1128/JVI.00379-14

Liao, S., Deng, D., Zhang, W., *et al.*, 2013. Human papillomavirus 16/18 E5 promotes cervical cancer cell proliferation, migration and invasion in vitro and accelerates tumor growth in vivo. *Oncol. Rep.*, **29**(1):95-102. http://dx.doi.org/10.3892/or.2012.2106

Liu, K., Lin, F.T., Ruppert, J.M., *et al.*, 2003. Regulation of E2F1 by BRCT domain-containing protein TopBP1. *Mol. Cell. Biol.*, **23**(9):3287-3304. http://dx.doi.org/10.1128/MCB.23.9.3287-3304.2003

Liu, Q., Guntuku, S., Cui, X.S., *et al.*, 2000. Chk1 is an essential kinase that is regulated by Atr and required for the G_2/M DNA damage checkpoint. *Genes Dev.*, **14**(12):1448-1459.

Longworth, M.S., Laimins, L.A., 2004. Pathogenesis of human papillomaviruses in differentiating epithelia. *Microbiol. Mol. Biol. Rev.*, **68**(2):362-372. http://dx.doi.org/10.1128/MMBR.68.2.362-372.2004

Longworth, M.S., Wilson, R., Laimins, L.A., 2005. HPV31 E7 facilitates replication by activating E2F2 transcription through its interaction with HDACs. *EMBO J.*, **24**(10):1821-1830. http://dx.doi.org/10.1038/sj.emboj.7600651

Lord, C.J., Ashworth, A., 2012. The DNA damage response and cancer therapy. *Nature*, **481**(7381):287-294. http://dx.doi.org/10.1038/nature10760

Matsuoka, S., Huang, M., Elledge, S.J., 1998. Linkage of ATM to cell cycle regulation by the Chk2 protein kinase. *Science*, **282**(5395):1893-1897. http://dx.doi.org/10.1126/science.282.5395.1893

Matt, S., Hofmann, T.G., 2016. The DNA damage-induced cell death response: a roadmap to kill cancer cells. *Cell. Mol. Life Sci.*, **73**(15):2829-2850. http://dx.doi.org/10.1007/s00018-016-2130-4

Maya, R., Balass, M., Kim, S.T., *et al.*, 2001. ATM-dependent phosphorylation of Mdm2 on serine 395: role in p53 activation by DNA damage. *Genes Dev.*, **15**(9):1067-1077. http://dx.doi.org/10.1101/gad.886901

McBride, A.A., 2013. The papillomavirus E2 proteins.

Virology, **445**(1-2):57-79. http://dx.doi.org/10.1016/j.virol.2013.06.006

McFadden, K., Luftig, M.A., 2013. Interplay between DNA tumor viruses and the host DNA damage response. *Curr. Top Microbiol. Immunol*., **371**:229-257. http://dx.doi.org/10.1007/978-3-642-37765-5_9

McKinney, C.C., Hussmann, K.L., McBride, A.A., 2015. The role of the DNA damage response throughout the papillomavirus life cycle. *Viruses*, **7**(5):2450-2469. http://dx.doi.org/10.3390/v7052450

McPhillips, M.G., Oliveira, J.G., Spindler, J.E., *et al*., 2006. Brd4 is required for E2-mediated transcriptional activation but not genome partitioning of all papillomaviruses. *J. Virol*., **80**(19):9530-9543. http://dx.doi.org/10.1128/JVI.01105-06

Mehta, K., Gunasekharan, V., Satsuka, A., *et al*., 2015. Human papillomaviruses activate and recruit SMC1 cohesin proteins for the differentiation-dependent life cycle through association with ctcf insulators. *PLoS Pathog*., **11**(4):e1004763. http://dx.doi.org/10.1371/journal.ppat.1004763

Melar-New, M., Laimins, L.A., 2010. Human papillomaviruses modulate expression of microRNA 203 upon epithelial differentiation to control levels of p63 proteins. *J. Virol*., **84**(10):5212-5221. http://dx.doi.org/10.1128/JVI.00078-10

Mighty, K.K., Laimins, L.A., 2011. p63 is necessary for the activation of human papillomavirus late viral functions upon epithelial differentiation. *J. Virol*., **85**(17):8863-8869. http://dx.doi.org/10.1128/JVI.00750-11

Miller, K.M., Tjeertes, J.V., Coates, J., *et al*., 2010. Human HDAC1 and HDAC2 function in the DNA-damage response to promote DNA nonhomologous end-joining. *Nat. Struct. Mol. Biol*., **17**(99):1144-1151. http://dx.doi.org/10.1038/nsmb.1899

Moiseeva, O., Mallette, F.A., Mukhopadhyay, U.K., *et al*., 2006. DNA damage signaling and p53-dependent senescence after prolonged β-interferon stimulation. *Mol. Biol. Cell*, **17**(4):1583-1592. http://dx.doi.org/10.1091/mbc.E05-09-0858

Moody, C.A., Laimins, L.A., 2009. Human papillomaviruses activate the ATM DNA damage pathway for viral genome amplification upon differentiation. *PLoS Pathog*., **5**(10):e1000605. http://dx.doi.org/10.1371/journal.ppat.1000605

Moody, C.A., Laimins, L.A., 2010. Human papillomavirus oncoproteins: pathways to transformation. *Nat. Rev. Cancer*, **10**(8):550-560. http://dx.doi.org/10.1038/nrc2886

Moody, C.A., Fradet-Turcotte, A., Archambault, J., *et al*., 2007. Human papillomaviruses activate caspases upon epithelial differentiation to induce viral genome amplification. *PNAS*, **104**(49):19541-19546. http://dx.doi.org/10.1073/pnas.0707947104

Munger, K., Howley, P.M., 2002. Human papillomavirus immortalization and transformation functions. *Virus Res*., **89**(2):213-228. http://dx.doi.org/10.1016/S0168-1702(02)00190-9

Munger, K., Werness, B.A., Dyson, N., *et al*., 1989. Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. *EMBO J*., **8**(13):4099-4105.

Myers, J.S., Cortez, D., 2006. Rapid activation of ATR by ionizing radiation requires ATM and MRE11. *J. Biol. Chem*., **281**(14):9346-9350. http://dx.doi.org/10.1074/jbc.M513265200

Myers, K., Gagou, M.E., Zuazua-Villar, P., *et al*., 2009. ATR and Chk1 suppress a caspase-3-dependent apoptotic response following DNA replication stress. *PLoS Genet*., **5**(1):e1000324. http://dx.doi.org/10.1371/journal.pgen.1000324

Nakahara, T., Tanaka, K., Ohno, S., *et al*., 2015. Activation of NF-κB by human papillomavirus 16 E1 limits E1-dependent viral replication through degradation of E1. *J. Virol*., **89**(9):5040-5059. http://dx.doi.org/10.1128/JVI.00389-15

Nelson, L.M., Rose, R.C., Moroianu, J., 2002. Nuclear import strategies of high risk HPV16 L1 major capsid protein. *J. Biol. Chem*., **277**(26):23958-23964. http://dx.doi.org/10.1074/jbc.M200724200

Nguyen, C.L., McLaughlin-Drubin, M.E., Munger, K., 2008. Delocalization of the microtubule motor dynein from mitotic spindles by the human papillomavirus E7 oncoprotein is not sufficient for induction of multipolar mitoses. *Cancer Res*., **68**(21):8715-8722. http://dx.doi.org/10.1158/0008-5472.CAN-08-1303

Nuovo, G.J., Wu, X., Volinia, S., *et al.*, 2010. Strong inverse correlation between microRNA-125b and human papillomavirus DNA in productive infection. *Diagn. Mol. Pathol*., **19**(3):135-143. http://dx.doi.org/10.1097/PDM.0b013e3181c4daaa

O'Connor, M., Bernard, H.U., 1995. Oct-1 activates the epithelial-specific enhancer of human papillomavirus type 16 via a synergistic interaction with NFI at a conserved composite regulatory element. *Virology*, **207**(1):77-88. http://dx.doi.org/10.1006/viro.1995.1053

O'Connor, M.J., 2015. Targeting the DNA damage response in cancer. *Mol. Cell*, **60**(4):547-560. http://dx.doi.org/10.1016/j.molcel.2015.10.040

O'Driscoll, M., Ruiz-Perez, V.L., Woods, C.G., *et al*., 2003. A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein (ATR) results in seckel syndrome. *Nat. Genet*., **33**(4):497-501. http://dx.doi.org/10.1038/ng1129

Offord, E.A., Beard, P., 1990. A member of the activator protein 1 family found in keratinocytes but not in fibroblasts required for transcription from a human papillomavirus type 18 promoter. *J. Virol*., **64**(10):4792-4798.

Oliveira, J.G., Colf, L.A., McBride, A.A., 2006. Variations in the association of papillomavirus E2 proteins with mitotic

chromosomes. *PNAS*, **103**(4):1047-1052. http://dx.doi.org/10.1073/pnas.0507624103

Park, J.S., Kim, E.J., Kwon, H.J., *et al*., 2000. Inactivation of interferon regulatory factor-1 tumor suppressor protein by HPV E7 oncoprotein. Implication for the E7-mediated immune evasion mechanism in cervical carcinogenesis. *J. Biol. Chem*., **275**(10):6764-6769. http://dx.doi.org/10.1074/jbc.275.10.6764

Patel, D., Huang, S.M., Baglia, L.A., *et al*., 1999. The E6 protein of human papillomavirus type 16 binds to and inhibits co-activation by CBP and p300. *EMBO J*., **18**(18): 5061-5072. http://dx.doi.org/10.1093/emboj/18.18.5061

Pearl, L.H., Schierz, A.C., Ward, S.E., *et al*., 2015. Therapeutic opportunities within the DNA damage response. *Nat. Rev. Cancer*, **15**(3):166-180. http://dx.doi.org/10.1038/nrc3891

Pedroza-Torres, A., Lopez-Urrutia, E., Garcia-Castillo, V., *et al.*, 2014. MicroRNAs in cervical cancer: evidences for a miRNA profile deregulated by hpv and its impact on radio-resistance. *Molecules*, **19**(5):6263-6281. http://dx.doi.org/10.3390/molecules19056263

Poddar, A., Reed, S.C., McPhillips, M.G., *et al*., 2009. The human papillomavirus type 8 E2 tethering protein targets the ribosomal DNA loci of host mitotic chromosomes. *J. Virol*., **83**(2):640-650. http://dx.doi.org/10.1128/JVI.01936-08

Reinson, T., Toots, M., Kadaja, M., *et al*., 2013. Engagement of the ATR-dependent DNA damage response at the human papillomavirus 18 replication centers during the initial amplification. *J. Virol*., **87**(2):951-964. http://dx.doi.org/10.1128/JVI.01943-12

Rincon-Orozco, B., Halec, G., Rosenberger, S., *et al.*, 2009. Epigenetic silencing of interferon-κ in human papillomavirus type 16-positive cells. *Cancer Res*., **69**(22):8718-8725. http://dx.doi.org/10.1158/0008-5472.CAN-09-0550

Ronco, L.V., Karpova, A.Y., Vidal, M., *et al*., 1998. Human papillomavirus 16 E6 oncoprotein binds to interferon regulatory factor-3 and inhibits its transcriptional activity. *Genes Dev*., **12**(13):2061-2072. http://dx.doi.org/10.1101/gad.12.13.2061

Sakakibara, N., Mitra, R., McBride, A.A., 2011. The papillomavirus E1 helicase activates a cellular DNA damage response in viral replication foci. *J. Virol*., **85**(17): 8981-8995. http://dx.doi.org/10.1128/JVI.00541-11

Satsuka, A., Mehta, K., Laimins, L., 2015. p38MAPK and MK2 pathways are important for the differentiation-dependent human papillomavirus life cycle. *J. Virol*., **89**(3):1919-1924. http://dx.doi.org/10.1128/JVI.02712-14

Scheffner, M., Werness, B.A., Huibregtse, J.M., *et al*., 1990. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell*, **63**(6):1129-1136. http://dx.doi.org/10.1016/0092-8674(90)90409-8

Scheffner, M., Huibregtse, J.M., Vierstra, R.D., *et al*., 1993. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. *Cell*, **75**(3):495-505. http://dx.doi.org/10.1016/0092-8674(93)90384-3

Sedman, J., Stenlund, A., 1995. Co-operative interaction between the initiator E1 and the transcriptional activator E2 is required for replicator specific DNA replication of bovine papillomavirus in vivo and in vitro. *EMBO J*., **14**(24):6218-6228.

Seebode, C., Lehmann, J., Emmert, S., 2016. Photocarcinogenesis and skin cancer prevention strategies. *Anticancer Res*., **36**(3):1371-1378.

Shreeram, S., Demidov, O.N., Hee, W.K., *et al.*, 2006. Wip1 phosphatase modulates ATM-dependent signaling pathways. *Mol. Cell*, **23**(5):757-764. http://dx.doi.org/10.1016/j.molcel.2006.07.010

Smith, J., Tho, L.M., Xu, N., *et al*., 2010. The ATM-Chk2 and ATR-Chk1 pathways in DNA damage signaling and cancer. *Adv. Cancer Res*., **108**:73-112. http://dx.doi.org/10.1016/B978-0-12-380888-2.00003-0

Smith, J.A., White, E.A., Sowa, M.E., *et al*., 2010. Genome-wide siRNA screen identifies SMCX, EP400, and Brd4 as E2-dependent regulators of human papillomavirus oncogene expression. *PNAS*, **107**(8):3752-3757. http://dx.doi.org/10.1073/pnas.0914818107

Song, S., Gulliver, G.A., Lambert, P.F., 1998. Human papillomavirus type 16 E6 and E7 oncogenes abrogate radiation-induced DNA damage responses in vivo through p53-dependent and p53-independent pathways. *PNAS*, **95**(5):2290-2295. http://dx.doi.org/10.1073/pnas.95.5.2290

Sorensen, C.S., Hansen, L.T., Dziegielewski, J., *et al*., 2005. The cell-cycle checkpoint kinase Chk1 is required for mammalian homologous recombination repair. *Nat. Cell Biol*., **7**(2):195-201. http://dx.doi.org/10.1038/ncb1212

Spardy, N., Duensing, A., Charles, D., *et al*., 2007. The human papillomavirus type 16 E7 oncoprotein activates the Fanconi anemia (FA) pathway and causes accelerated chromosomal instability in FA cells. *J. Virol*., **81**(23): 13265-13270. http://dx.doi.org/10.1128/JVI.01121-07

Spardy, N., Duensing, A., Hoskins, E.E., *et al*., 2008. HPV-16 E7 reveals a link between DNA replication stress, fanconi anemia D2 protein, and alternative lengthening of telomere-associated promyelocytic leukemia bodies. *Cancer Res*., **68**(23):9954-9963. http://dx.doi.org/10.1158/0008-5472.CAN-08-0224

Spardy, N., Covella, K., Cha, E., *et al*., 2009. Human papillomavirus 16 E7 oncoprotein attenuates DNA damage checkpoint control by increasing the proteolytic turnover of claspin. *Cancer Res*., **69**(17):7022-7029. http://dx.doi.org/10.1158/0008-5472.CAN-09-0925

Sperka, T., Wang, J., Rudolph, K.L., 2012. DNA damage

checkpoints in stem cells, ageing and cancer. *Nat. Rev. Mol. Cell Biol*., **13**(9):579-590. http://dx.doi.org/10.1038/nrm3420

Srivenugopal, K.S., Ali-Osman, F., 2002. The DNA repair protein, O^6-methylguanine-DNA methyltransferase is a proteolytic target for the E6 human papillomavirus oncoprotein. *Oncogene*, **21**(38):5940-5945. http://dx.doi.org/10.1038/sj.onc.1205762

Stanley, M.A., 2012. Epithelial cell responses to infection with human papillomavirus. *Clin. Microbiol. Rev*., **25**(2): 215-222. http://dx.doi.org/10.1128/CMR.05028-11

Steger, G., Corbach, S., 1997. Dose-dependent regulation of the early promoter of human papillomavirus type 18 by the viral E2 protein. *J. Virol*., **71**(1):50-58.

Stubenrauch, F., Hummel, M., Iftner, T., *et al*., 2000. The E8^E2C protein, a negative regulator of viral transcription and replication, is required for extrachromosomal maintenance of human papillomavirus type 31 in keratinocytes. *J. Virol*., **74**(3):1178-1186. http://dx.doi.org/10.1128/JVI.74.3.1178-1186.2000

Stunkel, W., Bernard, H.U., 1999. The chromatin structure of the long control region of human papillomavirus type 16 represses viral oncoprotein expression. *J. Virol*., **73**(3): 1918-1930.

Sun, Y., Jiang, X., Chen, S., *et al*., 2005. A role for the Tip60 histone acetyltransferase in the acetylation and activation of ATM. *PNAS*, **102**(37):13182-13187. http://dx.doi.org/10.1073/pnas.0504211102

Taniguchi, T., Garcia-Higuera, I., Xu, B., *et al*., 2002. Convergence of the fanconi anemia and ataxia telangiectasia signaling pathways. *Cell*, **109**(4):459-472. http://dx.doi.org/10.1016/S0092-8674(02)00747-X

Thomas, J.T., Hubert, W.G., Ruesch, M.N., *et al*., 1999. Human papillomavirus type 31 oncoproteins E6 and E7 are required for the maintenance of episomes during the viral life cycle in normal human keratinocytes. *PNAS*, **96**(15):8449-8454. http://dx.doi.org/10.1073/pnas.96.15.8449

Thomas, M., Narayan, N., Pim, D., *et al*., 2008. Human papillomaviruses, cervical cancer and cell polarity. *Oncogene*, **27**(55):7018-7030. http://dx.doi.org/10.1038/onc.2008.351

Thomas, M.C., Chiang, C.M., 2005. E6 oncoprotein represses p53-dependent gene activation via inhibition of protein acetylation independently of inducing p53 degradation. *Mol. Cell*, **17**(2):251-264. http://dx.doi.org/10.1016/j.molcel.2004.12.016

Thurn, K.T., Thomas, S., Raha, P., *et al*., 2013. Histone deacetylase regulation of ATM-mediated DNA damage signaling. *Mol. Cancer Ther*., **12**(10):2078-2087. http://dx.doi.org/10.1158/1535-7163.MCT-12-1242

Walker, M., Black, E.J., Oehler, V., *et al*., 2009. Chk1 C-terminal regulatory phosphorylation mediates checkpoint activation by de-repression of Chk1 catalytic activity. *Oncogene*, **28**(24):2314-2323. http://dx.doi.org/10.1038/onc.2009.102

Wallace, N.A., Galloway, D.A., 2014. Manipulation of cellular DNA damage repair machinery facilitates propagation of human papillomaviruses. *Semin. Cancer Biol*., **26**:30-42. http://dx.doi.org/10.1016/j.semcancer.2013.12.003

Wallace, N.A., Galloway, D.A., 2015. Novel functions of the human papillomavirus E6 oncoproteins. *Annu. Rev. Virol*., **2**(1):403-423. http://dx.doi.org/10.1146/annurev-virology-100114-055021

Wallace, N.A., Robinson, K., Howie, H.L., *et al*., 2012. HPV 5 and 8 E6 abrogate ATR activity resulting in increased persistence of UVB induced DNA damage. *PLoS Pathog*., **8**(7):e1002807. http://dx.doi.org/10.1371/journal.ppat.1002807

Wallace, N.A., Gasior, S.L., Faber, Z.J., *et al*., 2013. HPV 5 and 8 E6 expression reduces ATM protein levels and attenuates LINE-1 retrotransposition. *Virology*, **443**(1): 69-79. http://dx.doi.org/10.1016/j.virol.2013.04.022

Wallace, N.A., Robinson, K., Galloway, D.A., 2014. Beta human papillomavirus E6 expression inhibits stabilization of p53 and increases tolerance of genomic instability. *J. Virol*., **88**(11):6112-6127. http://dx.doi.org/10.1128/JVI.03808-13

Wallace, N.A., Robinson, K., Howie, H.L., *et al*., 2015. β-HPV 5 and 8 E6 disrupt homology dependent double strand break repair by attenuating BRCA1 and BRCA2 expression and foci formation. *PLoS Pathog*., **11**(3): e1004687. http://dx.doi.org/10.1371/journal.ppat.1004687

Wan, G., Mathur, R., Hu, X., *et al*., 2011. miRNA response to DNA damage. *Trends Biochem. Sci*., **36**(9):478-484. http://dx.doi.org/10.1016/j.tibs.2011.06.002

Wang, X., Wang, H.K., Li, Y., *et al.*, 2014. MicroRNAs are biomarkers of oncogenic human papillomavirus infections. *PNAS*, **111**(11):4262-4267. http://dx.doi.org/10.1073/pnas.1401430111

Wang, Y., Taniguchi, T., 2013. MicroRNAs and DNA damage response: implications for cancer therapy. *Cell Cycle*, **12**(1):32-42. http://dx.doi.org/10.4161/cc.23051

White, D.E., Negorev, D., Peng, H., *et al*., 2006. KAP1, a novel substrate for PIKK family members, colocalizes with numerous damage response factors at DNA lesions. *Cancer Res*., **66**(24):11594-11599. http://dx.doi.org/10.1158/0008-5472.CAN-06-4138

Wise-Draper, T.M., Wells, S.I., 2008. Papillomavirus E6 and E7 proteins and their cellular targets. *Front. Biosci*., **13**: 1003-1017. http://dx.doi.org/10.2741/2739

Wohlbold, L., Merrick, K.A., De, S., *et al.*, 2012. Chemical genetics reveals a specific requirement for Cdk2 activity in the DNA damage response and identifies Nbs1 as a Cdk2 substrate in human cells. *PLoS Genet*., **8**(8): e1002935. http://dx.doi.org/10.1371/journal.pgen.1002935

Wu, S., Shi, Y., Mulligan, P., *et al.*, 2007. A YY1-INO80 complex regulates genomic stability through homologous recombination-based repair. *Nat. Struct. Mol. Biol.*, **14**(12):1165-1172. http://dx.doi.org/10.1038/nsmb1332

Wu, S.Y., Lee, A.Y., Hou, S.Y., *et al*., 2006. Brd4 links chromatin targeting to HPV transcriptional silencing. *Genes Dev*., **20**(17):2383-2396. http://dx.doi.org/10.1101/gad.1448206

Yao, Z., Cui, Y., Watford, W.T., *et al.*, 2006. STAT5a/b are essential for normal lymphoid development and differentiation. *PNAS*, **103**(4):1000-1005. http://dx.doi.org/10.1073/pnas.0507350103

Yarden, R.I., Pardo-Reoyo, S., Sgagias, M., *et al*., 2002. BRCA1 regulates the G2/M checkpoint by activating Chk1 kinase upon DNA damage. *Nat. Genet*., **30**(3):285-289. http://dx.doi.org/10.1038/ng837

Zhang, R., Zhu, L., Zhang, L., *et al*., 2016. PTEN enhances G2/M arrest in etoposide-treated MCF7 cells through activation of the ATM pathway. *Oncol. Rep*., **35**(5):2707-2714. http://dx.doi.org/10.3892/or.2016.4674

Zhang, W., Hong, S., Maniar, K.P., *et al*., 2016. KLF13 regulates the differentiation-dependent human papillomavirus life cycle in keratinocytes through STAT5 and IL-8. *Oncogene*, **35**:5565-5575. http://dx.doi.org/10.1038/onc.2016.97

Zhang, Y., Cho, Y.Y., Petersen, B.L., *et al*., 2003. Ataxia telangiectasia mutated proteins, mapks, and RSK2 are involved in the phosphorylation of STAT3. *J. Biol. Chem*., **278**(15):12650-12659. http://dx.doi.org/10.1074/jbc.M210368200

Zhang, Y., Fan, S., Meng, Q., *et al*., 2005. BRCA1 interaction with human papillomavirus oncoproteins. *J. Biol. Chem*., **280**(39):33165-33177. http://dx.doi.org/10.1074/jbc.M505124200

Zhao, H., Jin, S., Fan, F., *et al*., 2000. Activation of the transcription factor Oct-1 in response to DNA damage. *Cancer Res*., **60**(22):6276-6280.

Zhou, B.B., Chaturvedi, P., Spring, K., *et al*., 2000. Caffeine abolishes the mammalian G_2/M DNA damage checkpoint by inhibiting ataxia-telangiectasia-mutated kinase activity. *J. Biol. Chem*., **275**(14):10342-10348. http://dx.doi.org/10.1074/jbc.275.14.10342

Ziv, Y., Bielopolski, D., Galanty, Y., *et al*., 2006. Chromatin relaxation in response to DNA double-strand breaks is modulated by a novel ATM- and KAP-1 dependent pathway. *Nat. Cell Biol*., **8**(8):870-876. http://dx.doi.org/10.1038/ncb1446

Zou, L., Elledge, S.J., 2003. Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes. *Science*, **300**(5625):1542-1548. http://dx.doi.org/10.1126/science.1083430

Zur Hausen, H., 2002. Papillomaviruses and cancer: from basic studies to clinical application. *Nat. Rev. Cancer*, **2**(5):342-350. http://dx.doi.org/10.1038/nrc798

Zur Hausen, H., 2009. Papillomaviruses in the causation of human cancers—a brief historical account. *Virology*, **384**(2):260-265. http://dx.doi.org/10.1016/j.virol.2008.11.046

中文概要

题　目：人类乳突病毒利用 DNA 损伤修复机制完成其生命周期

概　要：本文总结目前学术界对人类乳突病毒如何利用 DNA 损伤修复来完成其复制的认识。DNA 损伤修复对人类乳突病毒复制有不可或缺的作用。乳突病毒通过对许多 DNA 损伤因子的调控来控制病毒本身的复制。值得注意的是，病毒通过磷酸化 STAT-5 转录因子激活 ATM 和 ATR DNA 损伤修复通路，这意味着在乳突病毒复制的过程中，病毒利用对免疫反应的调节来激活 DNA 损伤修复机制，从而达到其复制的目的。

关键词：人类乳突病毒；DNA 损伤修复；扩展；分化；ATM/CHK2 通路；ATR/CHK1 通路；STAT-5 转录因子