ANNUAL REVIEWS

Annual Review of Virology

Virus DNA Replication and the Host DNA Damage Response

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Annu. Rev. Virol. 2018. 5:141–64

First published as a Review in Advance on July 11, 2018

The *Annual Review of Virology* is online at virology.annualreviews.org

https://doi.org/10.1146/annurev-virology-092917-043534

Keywords

DNA damage response, viral genome, virus replication, virus replication compartments, chromatin state

Abstract

Viral DNA genomes have limited coding capacity and therefore harness cellular factors to facilitate replication of their genomes and generate progeny virions. Studies of viruses and how they interact with cellular processes have historically provided seminal insights into basic biology and disease mechanisms. The replicative life cycles of many DNA viruses have been shown to engage components of the host DNA damage and repair machinery. Viruses have evolved numerous strategies to navigate the cellular DNA damage response. By hijacking and manipulating cellular replication and repair processes, DNA viruses can selectively harness or abrogate distinct components of the cellular machinery to complete their life cycles. Here, we highlight consequences for viral replication and host genome integrity during the dynamic interactions between virus and host.

1. INTRODUCTION TO VIRAL REPLICATION AND DNA DAMAGE RESPONSES

Chromatin: complex of macromolecules that packages DNA into a compact shape in cells; composed of DNA wrapped around histone proteins formed into nucleosomes

DNA damage response (DDR): network of cellular pathways that sense, signal, and repair DNA damage

Double-strand breaks (DSBs): when both strands of the DNA duplex are severed

ssDNA: single-stranded DNA

Cell cycle: the series of events that orchestrates genome replication and cell division in an organized fashion

The diversity of DNA virus genomes has led to a plethora of strategies for virus DNA replication. Each virus encodes a distinct set of proteins involved in replicating its genome. The smaller the viral genome, the more minimal the coding capacity, and the greater the need to harness cellular processes. Eukaryotic DNA replication is itself extensively regulated to ensure fidelity and coordination with surrounding chromatin (1). The cellular DNA damage response (DDR) is a complex network of signaling pathways that safeguards cellular DNA to maintain genomic integrity both during replication and when the cell is under threat from endogenous damage and exogenous agents (2–4). Activation of the DDR is triggered by damaged DNA lesions such as DNA double-strand breaks (DSBs) or accumulation of single-stranded DNA (ssDNA). Recognition of DNA damage leads to recruitment of cellular factors to repair the lesion and is coordinated with arrest of the cell cycle (**Figure 1**). It is now clear that these surveillance mechanisms that maintain integrity of the host cell genome can also respond to different forms of foreign genetic material delivered by virus infections. DNA viruses have evolved strategies to limit deleterious detection of their genomes by this host DNA repair machinery, while also exploiting components of these pathways to drive faithful replication of their genomes.

There are extensive interactions between viral DNA genomes and cellular pathways that detect and repair cellular DNA damage (**Table 1**). The interactions occur at multiple steps in the viral life cycle and have variable outcomes for productive viral DNA replication. Detection of viral genomes and activation of DDR signaling can occur at the initial steps of viral entry into the nucleus, during active viral DNA synthesis, during integration into the host genome, or during persistence of extrachromosomal viral genomes. Viral proteins can affect damage sensing and repair machinery by direct interactions with cellular components, by modulating cell cycle progression, or by inducing replication stress.

In this article we provide an overview of interactions recently uncovered between DNA virus replication and host DDR pathways. This is not intended to be an exhaustive review of this rapidly expanding topic. Many excellent reviews have recently summarized modulation of DNA damage signaling and repair pathways during viral transformation (5–9) and have outlined the current state of knowledge within individual viral families or viral families that are not covered by the scope of this review, such as hepatitis B viruses (10–16). Here, we present select examples of different viral genomes and focus on pathways redundantly targeted by DNA viruses during viral replication. Under each topic, we provide a section on potential consequences for both viral and host genomes, where we suggest how manipulating DDR pathways achieves the goal of virus propagation while also altering the genomic stability of the host.

2. PARTS AND PLAYERS

Host cell DNA replication is a tightly regulated process involving complex machinery that includes helicases to separate the DNA duplex, priming enzymes, and polymerases that synthesize nascent strands. In order to prevent genomic alterations and rearrangements, cells have evolved sophisticated mechanisms to detect DNA injuries, to signal responses that stop progression of the cell cycle, and to activate proper DNA repair pathways. Inaccurate repair leads to acquisition of cancer hallmarks that enable tumor cells to proliferate and disseminate, while inability to repair triggers apoptosis or senescence.

2.1. Detecting and Signaling DNA Damage

Sensor proteins, such as the MRE11-RAD50-NBS1 (MRN) complex and RPA, specifically detect damaged DNA by interacting with DSBs and ssDNA, respectively (**Figure 1**). The outcome of

damage sensing is activation of at least one of the three phosphatidylinositol-3-kinase-like kinases (PI3KKs)—ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3 related (ATR), or DNA-dependent protein kinase catalytic subunit (DNA-PKcs)—in order to transduce the injury into the DDR (3, 4). The DDR is driven by a series of phosphorylation events that orchestrate cellular processes such as DNA replication, DNA repair, and cell cycle control.

Recruitment of DNA repair proteins to DSBs is locally coordinated by ATM-dependent phosphorylation of effector proteins, followed by ubiquitination of chromatin surrounding the break (17). This cell cycle–regulated process triggers two main types of DNA repair: end joining and homologous recombination repair (HRR) (**Figure 2*a*,*b***). In the G_1 phase of the cell cycle, DSBs

Phosphatidylinositol-3-kinase-like kinases (PI3KKs): family of serine/threonine protein kinases that are involved in the DNA damage response; includes ATM, ATR, and DNA-PKcs

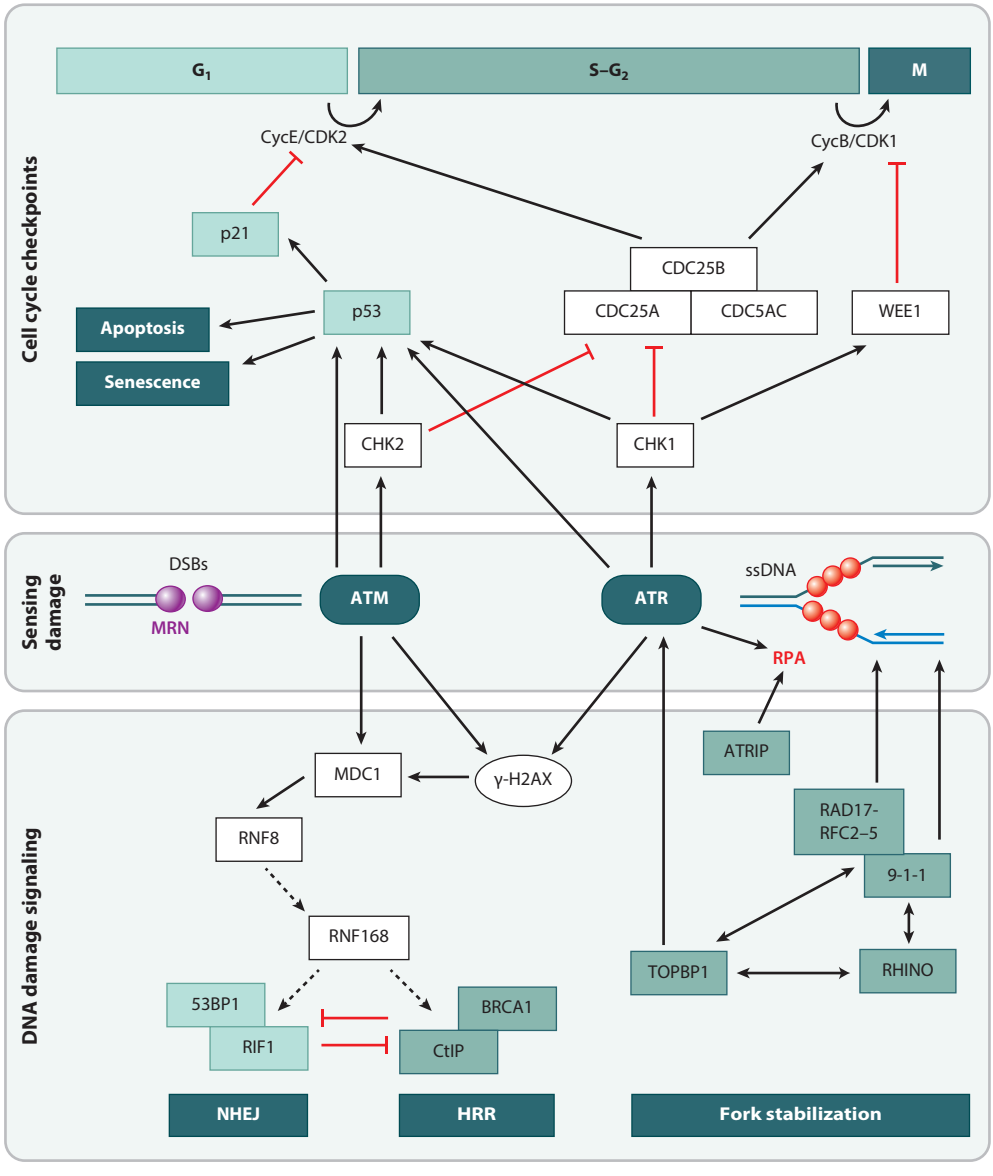

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Figure 1 (*Figure appears on preceding page*)

DNA damage responses to double-strand breaks (DSBs) and single-stranded DNA (ssDNA). (*Middle panel*) Sensing DNA damage. DNA DSBs are sensed by the MRN complex and signaled by activation of ATM. Accumulation of ssDNA at stalled or stressed replication forks triggers activation of ATR. Solid and dashed arrows indicate direct and indirect interactions, respectively. Proteins regulated in a cell cycle–dependent manner are color coded by the stage of the cell cycle at which they are activated. (*Lower panel*) DNA damage signaling is induced following activation of transducer kinases. Upon DSBs, phosphorylation of H2AX (γ-H2AX) initiates recruitment of MDC1, RNF8, and RNF168 in a hierarchal manner. In G_1, accumulation of 53BP1 and RIF1 at the break promotes repair by nonhomologous end joining (NHEJ). In S–G_2, homologous recombination repair (HRR) is promoted by the complex BRCA1-CtIP. At stalled/stressed forks, accumulation of RPA-coated ssDNA induces recruitment of ATRIP, the RAD17-RFC2–5 clamp loader and RAD9-RAD1-HUS1 (9-1-1) checkpoint clamps, and TOPBP1 at the fork. Full activation of ATR is achieved through its interaction with ATRIP and TOPBP1. (*Upper panel*) In order to prevent replication of damaged DNA, activation of DNA damage signaling is coupled with activation of cell cycle checkpoints that stop cell cycle progression. Both ATM and ATR activate checkpoint kinases (CHK2 and CHK1, respectively) in a phosphorylation-dependent manner. These kinases induce G_1–S checkpoint arrest by activating the tumor suppressor p53. The intra-S phase or G_2–M checkpoints are activated when the phosphatases cell division cycle 25 (CDC25) and WEE1 are inhibited by the checkpoint kinases.

are mainly repaired by canonical nonhomologous end joining (NHEJ), a process that religates DNA ends after limited end processing (2). In the S and G_2 phases, cells take advantage of the template created by newly replicated DNA to repair DSBs by HRR, in a faithful manner. In contrast to end-joining mechanisms, HRR is driven by extensive 5′-to-3′ end resection followed by guided synthesis of a new DNA. Structures generated through the process of strand exchange are resolved by the action of helicases or structure-selective endonucleases.

DNA repair pathway choice is dictated through regulation of proteins recruited at repair structures known as foci (2). Briefly, phosphorylation of histone variant H2AX (termed γ-H2AX) by ATM is read by the tandem BRCT domain of mediator MDC1 (**Figure 1**). Next, RNF8 recognizes ATM-dependent phosphorylation of MDC1 through its FHA domain and promotes polyubiquitylation of histone H1 (17). RNF168 binds directly to polyubiquitylated H1 and catalyzes recruitment of downstream factors, such as 53BP1, through monoubiquitylation of H2A (18). RNF168 also promotes accumulation of BRCA1 to sites of damage, although the mechanism is undefined. Both 53BP1 and BRCA1 accumulate at the break in a cell cycle–dependent manner (2). In G_1 phase, recruitment of 53BP1 and downstream effectors promotes NHEJ repair by antagonizing recruitment of the BRCA1-CtIP complex and thereby minimizing DNA end resection (**Figure 1**) (2). In S–G_2, CtIP cooperates with nucleases to facilitate extensive end resection (**Figure 2*b***). ssDNA exposed by this process leads to sequential recruitment of RPA, BRCA2-PALB2, and RAD51 proteins. During S phase, extensive ssDNA accumulation also arises when uncoordinated DNA unwinding and DNA synthesis occur at stalled replication forks or during fork reversal (4). Under these conditions, RPA-coated ssDNA triggers recruitment of the ATR-ATRIP kinase complex (**Figure 1**). Subsequently, ATR is fully activated through interaction with TOPBP1, a protein specifically recruited at junctions between ssDNA and double-stranded DNA (dsDNA) created upon replication of the lagging strand or by resected DNA ends upon fork reversal (4). Ultimately, removal or bypass of the roadblock that stalled the replication fork allows DNA polymerase to restart, and HRR mechanisms process DSBs that occur upon fork collapse (**Figure 2*c***).

These mechanisms for detection, signaling, and repair of DSBs as well as stalled forks are essential to safeguard genome integrity in the host cell. They are synchronized with activation of cell cycle checkpoints (through checkpoint kinases such as CHK1 and CHK2), specific transcriptional programs, and apoptosis (**Figure 1**). Since these pathways can directly interpret as DNA damage the unusual DNA structures within viral genomes (e.g., DNA hairpins within ssDNA molecules) or the DNA ends of linear dsDNA genomes (**Table 1**), they represent a threat for viral replication. Conversely, under the right conditions, they provide viruses with unique toolkits to

Ataxia telangiectasia mutated (ATM): protein kinase that is recruited and activated by double-strand DNA breaks to establish the DNA damage checkpoint

Ataxia telangiectasia and Rad3 related (ATR): related to ATM, this kinase responds to replication stress and activates cell cycle checkpoints

DNA-dependent protein kinase catalytic subunit (DNA-PKcs): combines with the Ku proteins to form the DNA-dependent protein kinase (DNA-PK), which is required for nonhomologous end joining

Homologous recombination repair (HRR): error-free DNA repair pathway that mediates the exchange of DNA strands of similar or identical nucleotide sequence

Table 1 Parts and players for viral replication and the DNA damage response

Virus				DNA damage response			
Genome	Type	Family	Players	Activated	Inhibited	Targeted players[b]	Reference(s)[a]
Linear ssDNA 	Adeno-associated virus	*Parvoviridae*	Rep, viral replication,[c] VRC[d]	ATM, ATR	—	ATM, DNA-PKcs, MRN, KU70-KU80	25–27, 29, 54, 99, 100
	Minute virus of mice	*Parvoviridae*	Viral replication[c]	ATM	ATR, Chk1	MRE11, p21	23, 24, 97, 113
Circular dsDNA 	Merkel cell polyomavirus	*Polyomaviridae*	L-TAg, viral replication, VRC	ATM, ATR	—	—	32, 102, 154
	Simian virus 40	*Polyomaviridae*	L-TAg, viral replication[c]	ATM, ATR	—	ATM, MRN, p53	30, 33, 103, 111
	JC polyomavirus	*Polyomaviridae*	Agnoprotein, viral replication[c]	ATM, ATR	NHEJ	KU70	31
	Human papillomavirus	*Papillomaviridae*	E1, E2, E6, E7, VRC	ATM, ATR	—	ATM, γ-H2AX, XRCC1, TOPBP1, RAD51, BRCA1, FANCD2, 53BP1, TIP60, CHK2, p53	36–41, 86, 105, 114, 115, 130, 153, 160, 161
Linear dsDNA 	Adenovirus	*Herpesviridae*	E1b55K-E4orf6, E4orf3, E1A	—	ATM, ATR, NHEJ	ATR, MRN, DNA-PKcs, TOPBP1, LIG4, p53, TIP60	56, 60–63, 108, 132
	Herpes simplex virus[e]	*Herpesviridae*	ICP0, ICP8-UL12, UL13, VRC	ATM	ATR, NHEJ	ATM, MRN, γ-H2AX, RNF8, RNF168, DNA-PKcs, PAXX KU70- KU80, ATR, ATRIP, RAP70, TOPBP1, PAR	27, 46–48, 68, 69, 77, 100, 108, 109, 118, 126, 129, 159
	Epstein-Barr virus[e]	*Herpesviridae*	EBNA3C, EBNA2/LP, BGL4, VRC	ATM, ATR	—	ATM, γ-H2AX, RAD51, BRCA1, RAD52, CHK1/ CHK2, p53, TIP60	50, 51, 80, 126
	Kaposi's sarcoma–associated herpesvirus[e]	*Herpesviridae*	LANA, vIRF1, v-cyclin, v-FLIP, VRC	ATR	ATM	ATM, γ-H2AX, MRN, ATR, DNA-PKcs, KU70-KU80, PARP-1, p53, TIP60	52, 76, 107, 120, 126–128
	Vaccinia virus	*Poxviridae*	VRC (cytoplasm)	—	—	MRN, DNA-PKcs	108, 116, 117

Abbreviations: dsDNA, double-stranded DNA; NHEJ, nonhomologous end joining; ssDNA, single-stranded DNA; VRC, viral replication compartment or center.

[a]Table was updated from lists made in previous reviews (5, 162).

[b]DNA damage response proteins that interact, are mislocalized, or are degraded by viral players.

[c]Induction of DNA damage response required viral replication or binding of a viral protein to origin of replication of the viral genome.

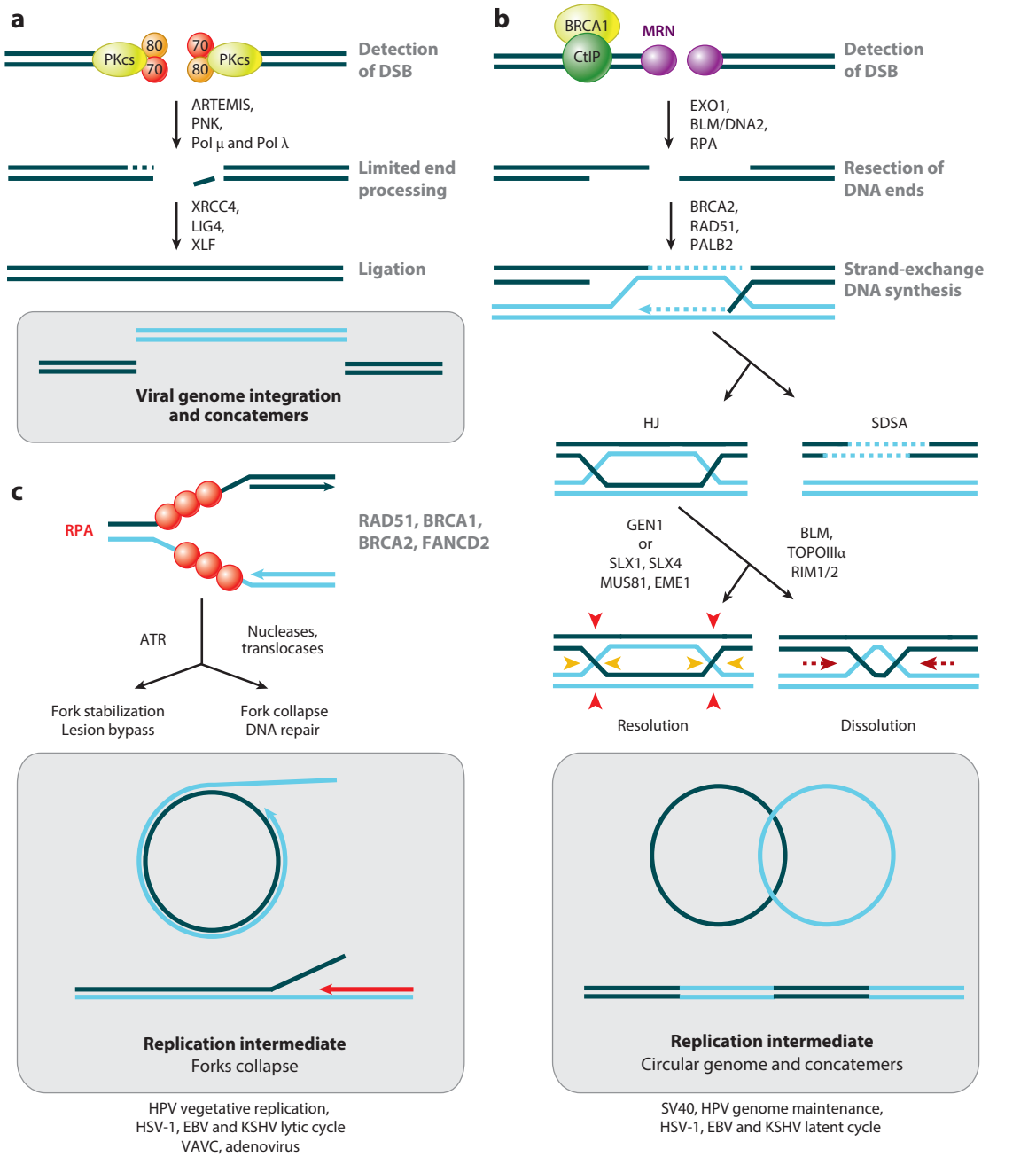
[d]Only upon coinfection with helper viruses.

[e]Genomes are maintained as episomes during latency.

promote successful viral DNA replication and enable resolution of different viral DNA replication intermediates that present exposed ssDNA or dsDNA ends (**Figure 2**).

2.2. Viral DNA Genome Configurations

The infectious virus life cycle includes a temporal cascade of viral gene expression. The first proteins to be expressed are from immediate early and early viral genes, which function to



HPV vegetative replication, HSV-1, EBV and KSHV lytic cycle VAVC, adenovirus

SV40, HPV genome maintenance, HSV-1, EBV and KSHV latent cycle

(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

DNA repair pathways—a toolkit for viral replication. (*a*) Classical nonhomologous end joining occurs through limited DNA end processing and religation. This repair pathway is thought to mediate viral genome integration into host genomes and can also affect concatemer formation. (*b*) Homologous recombination repair is triggered when DNA ends are extensively resected and coated with RPA. Subsequently, the recruitment of RAD51 by the action of BRCA1, BRCA2, and PALB2 leads to homology search and the formation of a displacement loop (D loop) upon invasion of the homologous template. D loops are resolved by synthesis-dependent strand annealing (SDSA) or by processing of a Holliday junction (HJ). The latter processes can be achieved through the actions of endonucleases (resolution) or by combining the activities of a helicase and a topoisomerase (dissolution). Many viruses have been reported to rely on homologous recombination repair to replicate. For example, the endonuclease activity of MRE11 as well as the resolvase processes intermediates created upon replication of circular genomes and concatemers. (*c*) Stalled or stressed replication forks can either restart or collapse. Stabilization of the fork by ATR enables the fork to bypass a DNA lesion and restart (4). Alternatively, the fork can be processed by nucleases (MRE11, DNA2, WRN, EXO1, CtIP) and translocases (ZRANB3, SMARCAL1). BRCA1, BRCA2, RAD51, and FANCD2 protect forks from extended resection in this process. This pathway is particularly important to support high levels of viral replication where viral helicases may be more prone to collapse. Virus abbreviations: EBV, Epstein-Barr virus; HPV, human papillomavirus; HSV-1, herpes simplex virus type 1; KSHV, Kaposi's sarcoma–associated herpesvirus; SV40, simian virus 40; VAVC, vaccinia virus.

promote viral gene expression and mediate viral DNA replication. Early viral proteins also frequently alter the host cell environment to promote viral replication by inactivating host factors and preventing their association with viral DNA, where they could limit gene transcription or replication. A common feature of virus replication systems is a viral DNA-binding protein that functions as an origin recognition factor and recruits proteins to initiate DNA synthesis. Larger viruses encode their own polymerases, helicases, and even proteins that participate in nucleotide synthesis.

DNA viruses have genomes that vary in the length and complexity of genes encoded (**Table 1**). The simplest DNA viruses are the parvoviruses, such as adeno-associated virus (AAV) and minute virus of mice, which have small ssDNA genomes of approximately 4.5–5.0 kb. The genome is flanked by inverted terminal repeats (ITRs), which initiate replication but may also attract host repair factors. With a single viral gene encoding nonstructural replication proteins (NS/Rep), these viruses are highly dependent on cellular factors (11, 12). Polyomaviruses are a family of viruses with similar sizes (approximately 5 kb), but the dsDNA genome is circular and is packaged as a minichromosome with cellular histones. Replication is orchestrated by a single multifunctional viral protein called the large tumor antigen (L-TAg) through binding to a specific DNA replication origin (10). Papillomaviruses have circular dsDNA genomes of approximately 8 kb, with a single replication origin contained within an upstream regulatory region. The early region encodes two replication proteins (E1 and E2) and three accessory proteins (E5, E6, and E7) that promote viral DNA replication and genome persistence by manipulating cellular pathways (19). Adenoviruses contain a dsDNA genome packaged as a linear molecule together with core viral proteins inside a nonenveloped particle. Adenoviruses encode three proteins required for viral DNA replication: an ssDNA-binding protein, a viral DNA polymerase, and a terminal protein that initiates protein-primed DNA replication through strand displacement (20). Herpesviruses have dsDNA genomes with various sizes: Herpes simplex virus type 1 (HSV-1) is approximately 152 kb, Epstein-Barr virus (EBV) is 172 kb, and Kaposi's sarcoma–associated herpesvirus (KSHV or HHV-8) is approximately 140 kb. HSV-1 encodes seven essential replication proteins and possesses three origins of replication. Herpesviruses are thought to replicate by a rolling circle mechanism from circularized genomes to generate long linear DNA concatemers, but the mechanism underlying the formation of the concatemers is unclear. It has also been suggested that HSV-1 DNA replication occurs via a recombination-dependent mechanism (14).

Nonhomologous end joining (NHEJ): the repair of double-strand DNA breaks by direct ligation of broken ends; does not require homology

dsDNA: double-stranded DNA

Checkpoints: control mechanisms that ensure proper division of the cell and occur at the G_1–S, intra-S, and G_2–M boundaries

Parvoviruses: nonenveloped viruses (18–28 nm) with linear single-stranded DNA genomes (~4.5–5.0 kb) with hairpin structures at either terminus that cause lytic infections

Polyomaviruses: nonenveloped viruses (40–50 nm) with circular double-stranded DNA genomes (~5.0 kb) that can cause cellular transformation and cancer

3. VIRAL ACTIVATION AND MODULATION OF DNA DAMAGE RESPONSE SIGNALING

Papillomaviruses: nonenveloped viruses (50–60 nm) with circular double-stranded DNA genomes (~8 kb); high-risk papillomaviruses cause cellular transformation and cancer

Adenoviruses: nonenveloped viruses (90–100 nm) with double-stranded DNA genomes (~26–48 kb) that cause lytic infections

Herpesviruses: enveloped viruses (120–300 nm) with linear double-stranded DNA genomes (~140–170 kb) that cause lytic or latent infections

Many viruses activate distinct virally induced signaling pathways involving DDR kinases, but these pathways are different from canonical signaling in response to genomic DNA damage. It can be hard to distinguish whether DDR signaling activated during infection represents a cellular response to the stress of viral replication or whether it is an active process induced by virus to promote efficient replication. In some cases, components of the DDR network have detrimental impacts on viral replication, suggesting they form an intrinsic antiviral defense. Conversely, there are many scenarios where virally induced DDR signaling is a necessary part of reprogramming of the nuclear environment that facilitates viral appropriation of cellular functions.

3.1. Activating DNA Damage Response Signaling

Even the simple parvoviruses have undergone complex interactions with the DDR network (11, 21). Autonomous parvoviruses induce cell cycle arrest and then exploit the cellular environment for conversion of the linear ssDNA viral genomes into dsDNA templates for replication. Some, such as B19V, induce broad DDR signaling with multiple PI3KKs activated that contribute to downstream signaling (22). In contrast, minute virus of mice activates ATM signaling (23) but also prevents full ATR activation and signaling through Chk1 (24). DDR signaling appears to aid viral replication (22, 23), although it is unclear the degree to which DDR signaling results from replication stress, impacts on the cell cycle, or nuclease activity of viral nonstructural proteins. The AAV parvovirus depends upon helper functions provided by coinfection with an adenovirus or HSV. During productive AAV replication with an adenovirus as helper, signaling is through DNA-PKcs (25, 26), whereas with HSV-1 as helper, it is mainly through ATM (27). Interestingly, the MRN complex binds to the AAV ITR, where it may have detrimental effects on replication (28) but promotes viral DNA integration (29). These observations from the simplest end of the viral genome spectrum highlight how viruses have evolved different strategies to adapt to their host cell environment.

The polyomaviruses have provided powerful tools to study DNA replication. Initial interactions may be through L-TAg, which modulates the host environment by deregulating cell cycle and transcriptional profiles. This leads to upregulation of DDR factors and can activate ATM- and ATR-dependent signaling, as seen for simian virus 40 (SV40) (30), JC polyomavirus (31), and Merkel cell polyomavirus (32). Interaction of L-TAg with the viral origin drives viral DNA synthesis, which also contributes to DDR signaling (31, 33, 34). The impact of these DDR pathways on virus replication varies by species. Inhibiting ATM and ATR kinases limits replication, since L-TAg is a substrate for ATM phosphorylation (35) and the kinases affect the resolution of viral replication intermediates (33).

Another example of exploitation of DDR signaling is provided by human papillomaviruses (HPVs), where ATM and repair factors play essential roles in vegetative viral replication (9, 36–39). HPVs induce DDR signaling in differentiated cells in order to harness repair factors to replicate viral DNA. High-risk cancer-inducing HPVs induce constitutive ATM kinase activation and phosphorylation of downstream effectors (9). This may help to create the G_2-arrested cellular environment required for amplification of viral genomes. It is unclear what triggers ATM activation, since there are no free DSBs, and the mechanism may not involve canonical MRN-dependent signaling (36). When expressed alone, both E1 and E7 viral proteins can induce ATM, potentially through replication stress on the host genome (40–42).

Larger viruses have a more complex association with DDR signaling pathways. For example, HSV-1 infection results in activation of ATM kinase activity, which appears beneficial for virus

replication (43, 44), but the ATR signaling pathway is inhibited (45–47). Although ATR-CHK1 signaling is not activated, components of this pathway are recruited to viral replication sites and may be beneficial for HSV-1 infection (46, 48). ATM signaling is also implicated in EBV lytic replication (49), but it is unclear whether ATM is required to generate a replication-competent cellular environment or to promote lytic gene expression (13). EBV primary infection of B cells leads to activation of ATM-CHK2 signaling (50). Replication stress and ATR activation in early proliferating cells may also limit nucleotide pools and restrict EBV immortalization (51). There is a complicated relationship between activation of the PI3KKs during KSHV infection, which may reflect differences in infected cell types (15, 52).

3.2. Manipulating DNA Damage Response and DNA Repair Components

Despite these examples of harnessing the apparent benefits of DDR signaling, there are scenarios where activation of the damage kinases is detrimental for virus DNA replication. A now classic example comes from adenovirus, where the MRN complex is targeted in redundant ways by early viral proteins from the E1 and E4 regions to prevent activation of the DDR and processing of the viral genome (53–57). Adenovirus proteins also target DNA-PKcs (58) and DNA ligase IV (59) to inhibit the NHEJ pathway. ATR signaling can be inhibited during adenovirus infection by targeting either MRN (60) or TOPBP1 (61). It has also been suggested that at least in some cell types, adenovirus replication induces noncanonical local DDR signaling that prevents DNA replication of mutant viruses (53, 62). It is intriguing that activation of signaling damage kinases may be highly nuanced even in a conserved viral family, with variability between serotypes suggesting different strategies to combat DDR and repair (61, 63, 64).

Viral genomes can be recognized upon release from virus particles in infected nuclei (65, 66). Cellular sensors respond to viral genomes, and defensive host complexes are assembled into structures at the sites associated with incoming viral genomes. The HSV-1 genome is thought to be delivered into the nucleus as a linear molecule with nicks and single-strand gaps (67), which could attract repair factors. Among the intrinsic host defenses that assemble at sites of incoming HSV-1 genomes are components of the DDR (68). Early responses to the HSV-1 genome are quickly counteracted by the E3 ubiquitin ligase ICP0, which antagonizes intrinsic host defenses. Early DDR markers such as γ-H2AX and MDC1 are found at sites of incoming viral genomes, but recruitment of downstream repair proteins such as 53BP1 is prevented by ICP0-mediated degradation of RNF8 and RNF168 (69). This selective disarming suggests that upstream DDR factors may be exploited, potentially for recombination-mediated replication, whereas downstream proteins are excluded, potentially to prevent processing or silencing of viral genomes. Other intrinsic defenses that are targeted by ICP0 include components of PML nuclear bodies and the sensor IFI16, which are also associated with DNA damage and repair (70, 71). Herpesviruses produce other proteins that selectively modulate DDR and repair pathways during either lytic or latent phases of the life cycle. For example, the HSV-1 viral ssDNA-binding protein ICP8 forms a complex with the viral UL12 exonuclease, and together they stimulate recombination-dependent replication through single-strand annealing and resection to inhibit other forms of end joining (72). Degradation of DNA-PKcs by the ICP0 ligase activity (73) may also prevent end joining of viral genomes to promote viral replication.

3.3. Consequences

The specific stage of the cell cycle when damage is sensed will determine outcomes of DDR signaling in response to cellular DNA damage (**Figure 1**) (2). Cell cycle status also affects viral replication and is manipulated by virus infection. Viral oncoproteins frequently target the tumor

suppressor pRb, which results in free E2F transcription factor to promote S phase entry (9). Virally induced cell cycle progression allows DNA viruses to optimize access to the cellular replication machinery available during S phase. An alternative strategy is to activate DDR signaling in G_2, when there is no competition with host DNA synthesis. Viral dysregulation of cell cycle, DNA damage signaling, and repair pathways also has functional consequences for host genome integrity.

3.3.1. When the DNA damage response dictates the viral life cycle. A characteristic feature of herpesviruses is dual phases of lytic infection and persistent latent infection. In latency, the viral genome persists without progeny production in specific cell types, such as neurons for HSV-1 and B cells for EBV. It is possible that DDR pathways contribute to the establishment of latency and are manipulated during reactivation (74). Since DDR signaling is important during lytic infection, differences in DDR pathways in certain cell types could push infection toward latency. For example, HSV-1 infection of neurons may not activate DDR signaling to the same extent as infection of non-neuronal cells (43). Degradation of RNF8 and RNF168 by ICP0 prevents ubiquitinylation of histones and recruitment of downstream repair factors (69), which could contribute to silencing of viral genomes during establishment of latency in neurons, where ICP0 levels are lower (75). KSHV infection of primary endothelial cells induces ATM and γ-H2AX early during infection, which may be important for latency establishment (76). DDR factors may also play roles at late stages of infection. For example, DDR signaling could be coupled to nuclear egress by recruiting the egress complex component UL31 through poly-ADP ribose binding (77).

3.3.2. Threats to stability of host genomes. Genomic instability in virally induced tumors could be driven by viral replication stress–induced DNA damage, inhibition of DNA damage checkpoints, random viral DNA integration, or amplification and structural arrangement of integrated viral DNA. The DDR can act as an innate tumor suppressor, and DDR manipulation may therefore contribute to transformation during herpesvirus infection (78). For example, the EBV latent protein EBNA3C attenuates ATM-CHK2 signaling to enable hyperproliferation and immortalization of B cells (50). Persistent DDR foci have also been observed in senescent EBV-infected B cells that provide a barrier to outgrowth during transformation (51). Other EBV gene products that drive oncogenesis independently target cellular functions involved in maintenance of genome integrity (13, 79, 80). HPV are another example of viruses that trigger instability through collateral damage. In HPV-associated malignancy, genomic instability generates numerical and structural chromosome abnormalities (81) and micronuclei (82). This arises as a result of the expression of the E6 protein, which inactivates the p53 tumor suppressor pathway, as well as the E7 protein, which interferes with the tumor suppressor pRb pathway and induces centrosome duplication error (9, 83). Inactivation of these cellular checkpoints triggers unscheduled S phase entry of differentiated keratinocytes to enable vegetative amplification of the viral genome but also directly threatens host genome integrity (9, 84). The combined action of E6 and E7 also triggers replication stress and associated DNA damage to cellular DNA by significantly reducing nucleotide pools (85). The Fanconi anemia repair protein FANCD2, which protects stalled replication forks, specifically accumulates at HPV replication foci (86), and depletion of FANCD2 predisposes HPV E7 transgenic mice to head and neck cancer (87). These findings suggest that replication stress is an active driver of HPV-induced tumorigenesis. Studies of HPV tumors revealed random integration into DNA repair genes, providing an additional driver for genomic instability (84, 88, 89). Replication of integrated HPV genomes may also contribute to induction of focal genomic instability by rearrangements between integrated copies (90). Although mechanisms behind this phenomenon are still unclear, current models propose that viral DNA replication and host DNA repair pathways participate in this process (90, 91). Viral genome integration is a

recurrent theme in virally induced cancers (92), suggesting similar processes may contribute to acquisition of genomic instability in other nonviral cancers.

4. VIRAL REPLICATION CENTERS

Viral replication compartments or centers (VRCs): specific locations where viral and cellular proteins required for replication are concentrated to promote viral gene expression and replication

Cellular DNA replication takes place at discrete nuclear foci where replication proteins localize. In contrast, viral DNA replication occurs within distinct virus-induced structures that have been referred to as viral replication compartments or centers (VRCs) (93–96). Both viral and cellular proteins concentrate at these VRCs and aid viral gene transcription and DNA replication. Among the cellular factors recruited to promote virus infection are proteins involved in cellular DNA replication and repair. In contrast, some potentially detrimental host proteins are actively sequestered away from sites of viral DNA synthesis. Each virus has a distinct set of cellular factors that are either harnessed or inactivated, and these may differ even within highly conserved viral families. The challenge of defining host proteins that are harnessed or inactivated by DNA viruses has been facilitated by proteomic approaches that identify proteins associated with replicating viral genomes.

4.1. Recruiting and Harnessing DNA Repair Machinery

Studies from the simplest viral systems to the more complex have revealed many host replication and repair factors selectively recruited to VRCs. For example, autonomous parvoviruses establish replication factories called APAR bodies, where cellular replication and repair proteins localize together with viral nonstructural replication proteins (12, 22, 97). In contrast, AAV replicates only when its helper virus establishes a cellular environment conducive to replication, including formation of VRCs where AAV colocalizes (98). DDR components accumulate at these shared sites, including activated ATM and DNA-PKcs (26, 27). Replication compartments formed by expression of Rep protein with the viral ITR as the replication origin also accumulated DNA-PKcs and Ku proteins (26), which could reflect direct interactions with ITR or Rep protein (99, 100). Cellular repair proteins localize at polyomavirus sites dependent on the L-TAg and viral replication (32, 33, 101–103). Inhibition of ATM and ATR kinases limits formation of these discrete polyomavirus replication foci (32). Although there is robust activation of the downstream kinases CHK1 and CHK2, their kinase activity may not be required for polyomavirus replication (104). In HPV-positive cells, DDR proteins involved in both DNA recombination and fork protection (e.g., MRN, BRCA1, ATRIP, RAD51, FANCD2, and CHK2) accumulate at sites of viral genome replication (36, 37, 86, 91, 105). Recruited factors may facilitate productive viral replication through recombination or processing of viral DNA structures. The HPV replication proteins E1 and E2 also form nuclear viral replication foci when coexpressed and recruit many host DNA repair factors (105). This selective activation and accumulation of DDR factors may be crucial for these small viruses to orchestrate their takeover of cellular functions.

Numerous DNA repair proteins have been found at VRCs for herpesviruses, either during lytic replication or upon reactivation from a latent state. Herpesviruses generate large globular compartments through ordered assembly with viral and cellular proteins. Both the MRN sensor and the Ku70-Ku80 complexes are located at VRCs with HSV (43, 44, 106) and KSHV (107), but downstream HRR proteins are not consistently found within these viral structures. Therefore, the roles of most of these proteins in viral DNA replication are not clear. Cellular proteins in VRCs have been identified by pulldown of the viral replication protein (106) or affinity purification of proteins associated with newly replicated, labeled viral DNA (108–110). These approaches identified factors in DNA replication, gene transcription, RNA processing, and chromatin remodeling,

as well as repair factors, including MRN and ATM. Additional pathways identified include mismatch repair and base excision repair. These proteomic approaches provide a comprehensive view of cellular DNA replication and repair factors that are potentially harnessed by virus infection.

4.2. Removing Harmful Factors

Host factors that have detrimental effects on viral replication can be disarmed through targeted degradation or mislocalization. In some systems, activation of ATM signaling could influence DDR factor recruitment and DSB repair pathway choice for the viral genome. For example, the ATM kinase is suggested to block recruitment of NHEJ factors to replicating SV40 viral DNA, and this could prevent concatemerization of the viral genome, which would disrupt productive viral DNA replication (111). This is seen at VRCs for SV40, where ATM promotes recruitment of resection enzymes, but its inhibition results in accumulation and activation of DNA-PKcs and NHEJ factors (111). Although the MRN complex is exploited by a number of viruses, it can also have detrimental effects for other viruses and is specifically excluded from VRCs. This was first observed with adenovirus type 5, where the MRN complex is targeted for degradation by E4orf6-E1b55K and is mislocalized away from VRCs by the E4orf3 protein (55, 112). When these early gene products are not expressed, MRN appears at VRCs, where it inhibits viral DNA replication and results in formation of joined viral concatemers (54–57). The mechanism for inhibition of DNA replication is not completely clear, but the MRN complex binds to viral genomic DNA (53, 56). There is also selective manipulation of DDR proteins by some parvoviruses, with depletion of MRE11 (23) and p21 (113) to ensure a premitotic state that facilitates viral replication. A more comprehensive view of factors associating on viral genomes will be provided by proteomic approaches, and these will provide insights into the selective recruitment as well as the potentially harmful factors targeted by early viral antagonists.

4.3. Consequences

It is still unclear how global disruption of nuclear architecture induced during virus lytic infection alters host cell functions. Cellular factors accumulated at VRCs may represent specific attractions for viral benefit or may be merely brought along as part of multisubunit complexes. Sequestering DDR factors at VRCs could physically prevent their ability to respond to host DNA damage and thus increase genomic instability.

4.3.1. Impacts of viral replication centers on cellular functions. The extent to which DDR factors are sequestered in VRCs to participate in viral genome replication or, rather, to interfere with their cellular function is not clear. Virally induced replication stress translates into reduced cellular DNA fork rates (85), which may activate ATR signaling and contribute to productive viral replication or viral plasmid genome maintenance. Infection may also affect levels and functions of host repair factors. For example, expression of DDR proteins increased during HPV infection or expression of viral oncogenes (114, 115). It has been suggested that E7 protein is sufficient to activate the DDR by increasing the half-life of repair factors necessary to promote viral replication (114). The MRN complex is recruited into VRCs for many viruses. Depletion of MRN decreases herpesviral DNA replication for HSV-1 (43) and KSHV (107). This could be due to its effects on ATM activation. Alternatively, the MRN exonuclease activity appears to have some important role based on observations with a specific inhibitor during KSHV reactivation (107). If recombination promotes herpesvirus replication, NHEJ would conversely have an inhibitory effect on replication, which would explain why the virus targets factors in this pathway. DNA-PKcs inhibition or Ku80 knockdown increased KSHV lytic replication (52). There is also the chance for indirect effects

on the host genome as a result of detrimental cellular factors being inactivated to minimize their association with replicating viral genomes.

4.3.2. Cross talk with innate immune responses. Although most DNA viruses replicate in the nucleus, there is also a role for preventing genome sensing in the cytoplasm. Poxviruses replicate their DNA genomes at cytoplasmic factories where viral replication proteins colocalize with cellular factors. Among host factors that accumulate at these cytoplasmic sites are some with roles in cell replication and repair, such as topoisomerase and PCNA (108, 116). Interestingly, also found at these cytoplasmic VRCs are DNA damage sensors such as MRN (108) and DNA-PKcs (117). The observation that DNA repair proteins accumulate at cytoplasmic VRCs of poxviruses suggests cytoplasmic functions that are counteracted by viruses. For example, members of the MRN complex have been implicated in innate immune responses to foreign DNA as cytoplasmic DNA sensors for NF-κB activation (117–119). Truncated forms of the LANA protein of KSHV can be located in the cytoplasm, where they associate with MRE11-RAD50 and can modulate the NF-κB pathway, potentially affecting lytic reactivation (120). Other viral proteins that interact with MRN appear in the cytoplasm, although it has not yet been determined whether these interactions directly alter innate responses. For example, the adenovirus E1b55K and E4orf3 proteins both localize with MRN in cytoplasmic aggregates (121, 122), and HSV-1 ICP0 also has a cytoplasmic function (123). Intriguingly, these viral proteins also target DNA-PKcs (58, 73) and PML (70, 71, 124), suggesting common targets for antagonists of sensing pathways in DNA repair and innate immunity.

5. PLAYING WITH CHROMATIN

Cellular DNA is compactly wrapped around the nucleosome, the smallest subunit of chromatin. Nucleosomes are composed of histones and histone variants, decorated with a myriad of post-translational modifications dynamically placed or removed by cellular enzymes (chromatin writers and erasers, respectively). Importantly, chromatin reader proteins interpret specific posttranslational modification combinations and translate them into biological processes such as chromatin compaction, transcription, DNA repair, and activation of immune responses (17, 125). Viruses have evolved strategies to commandeer chromatin-associated processes on both viral and cellular genomes, with impacts for damage responses on both.

5.1. Rewiring and Mimicking Histone Modifiers

The γ-H2AX mark is observed during many viral infections and is detected at VRCs with HPV, EBV, and KSHV DNA (**Table 1**). Phosphorylation of H2AX is achieved by cellular PI3KKs of the DDR and also by virally encoded mimics (7, 126). All herpesviruses examined, including HSV-1, EBV, and KSHV, induce γ-H2AX during lytic replication (52, 127, 128), although it may be dispensable for HSV-1 replication (129). During KSHV infection, γ-H2AX colocalizes with viral LANA protein and is suggested to contribute to association with viral terminal repeats for episome persistence (128). During productive replication of HPV, γ-H2AX accumulates on viral genomes, consistent with a model where DDR is activated to process replication intermediates (37).

In addition to direct chromatin effects, viruses induce indirect effects as a result of rewiring of histone modifiers. For example, herpesviruses, polyomaviruses, and HPVs target the histone acetyltransferase TIP60 for phosphorylation or degradation. During EBV infection, TIP60 is essential for EBV-induced DDR signaling to promote efficient replication (126). Interestingly, TIP60 is phosphorylated by virally encoded kinases from HSV-1, EBV, and KSHV (126). During HPV infection, Tip60 plays a dual role: participating in E2-mediated repression of the viral oncogenes E6 and E7 during establishment and maintenance of the viral genome, and then contributing

to amplification of HPV genomes in the upper epithelium (130, 131). In adenovirus infection, TIP60 binding to viral genomes represses early gene transcription; adenovirus therefore evolved to target its proteasomal degradation (132). TIP60 thus provides one example of how a chromatin modifier can be selectively manipulated by viruses, with implications for DDR on both host and viral genomes.

The state of the viral DNA when it is uncoated and delivered into the nucleus will affect sensing and DDR activation by host machinery. The adenovirus genome is packaged into particles without any cellular proteins, and viral DNA enters the nucleus wrapped only with core viral proteins (133). Protein VII is one of the core basic proteins, and it is thought to protect incoming viral DNA from recognition and DDR activation (134). Newly synthesized protein VII can also associate with cellular chromatin, where it sequesters cellular factors to overcome host responses (135, 136). One cellular factor bound by protein VII is SET, a protein that affects access of repair proteins to chromatin (137) and could be harnessed by adenovirus to abrogate the DDR on host and/or viral genomes (135). At least some fraction of replicating adenovirus genomes possess histones in nucleosomes (133), but these nucleosomes may not completely resemble that of host chromatin. In some cell lines, adenovirus replication leads to γ-H2AX phosphorylation, but this is not assembled on the viral genome and is not associated with formation of DDR foci (53).

5.2. Chromatin in Genome-to-Genome Interactions

The DDR network and chromatin status can jointly affect how viral genomes interact with the resident cellular genome. Integration into the host genome provides an attractive strategy to ensure persistence of the viral genome to take advantage of host transcriptional machinery. Alternatively, a number of DNA viral genomes are maintained as extrachromosomal episomes, in some cases tethered to host chromatin to ensure partitioning during cell division (138). For example, after several rounds of DNA synthesis, the HPV genome establishes persistence at a low copy number (139). This ensures efficient segregation of the genome to daughter cells during cell division and requires association with host chromatin. Tethering of the episome is mediated by viral E2 protein, which connects viral DNA to chromatin through cellular factors such as the BRD4 chromatin adaptor (139). The KSHV genome is also maintained as a dsDNA circular episome in the nucleus during latency (140). The viral LANA protein promotes latency through active repression of lytic genes as well as by tethering the viral episome to host DNA through interaction with chromatin in tumor cells. It has also been suggested that H2AX and its phosphorylation are important for LANA tethering (128). Latency and productive replication are also dictated by the state of chromatin on the viral genome. Since chromatin modifiers have different expression levels among various cell types, they may affect permissiveness for viral replication (141). During latency, LANA of KSHV and EBNA-1 of EBV maintain chromatinized viral episomes near heterochromatic regions of the host cell genome (140, 142–145). Different types of stimuli open up chromatin during reactivation, and DNA damage signaling could have a role during this process (126, 146).

5.3. Consequences

Chromatin state is central to sensing and repair of DNA damage, since both chromatin compaction and histone posttranslational modifications define outcomes. For example, the TIP60-KAT5 complex stimulates DSB signaling and fine-tunes DNA repair pathway choice by acetylating ATM and histones (125, 147, 148). Heterochromatin represents a barrier for DNA repair, and highly open chromatin is more prone to genomic instability (149). Therefore, direct or indirect effects of virus infection on chromatin dynamic states may alter pathways that safeguard genomic integrity.

5.3.1. Direct and indirect interactions with chromatin. In order to regulate epidermal differentiation and promote replication of HPV in differentiated keratinocytes, the viral E7 manipulates histone lysine methylation through activation of the histone methyl transferase EZH2 and the histone demethylases KDM6A and KDM6B (150). While modulation of histone lysine modification promotes productive viral genome replication, the addiction of HPV-positive cancer cells to demethylase expression suggests they also contribute to tumorigenesis (151).

Targeting histone modifiers can have impacts beyond direct effects on chromatin. In addition to repair roles, the TIP60 complex also regulates key tumor suppressors and oncogenes such as p53, Rb, and MYC (152). Viruses that target TIP60 for degradation or relocalization on chromatin therefore also influence checkpoints. HPV E6 hijacks the UBR5 E3 ligase to downregulate TIP60-KAT5 levels and promotes cell survival in cancer cells (153). A recent study also suggests that Merkel cell polyomavirus viral proteins can alter composition of the NuA4-TIP60 complex for cellular transformation (154). Whether such activity is also required for viral replication remains to be investigated.

Integration into host chromosomes can represent a dead-end pathway for the viral genome, because it prevents further replication and progeny production. This is the case with papillomaviruses, where disruption of E1 or E2 prevents viral genome replication. This also results in loss of repression of the E6 and E7 viral promoters, which provide selective advantages in cancer cells (9). Accidental integration of viral genetic material into the host genome may exploit common fragile sites, where DDR components accumulate at slow-replicating regions of the cellular genome to maintain integrity. Viruses may hijack this association to gain access to factors beneficial for amplification of viral DNA (155), but these factors may also facilitate recombination and integration of viral DNA.

5.3.2. Avoiding antiviral effects of chromatin. Viruses employ different strategies to protect their genomes from chromatin-driven intrinsic immunity, including avoidance of histone deposition. Since chromatin modifications are key to cellular DNA damage and repair, preventing histone deposition or nucleosome formation on viral genomes may limit docking of detrimental repair factors. This strategy has been suggested to occur during KSHV lytic infection (107) and may explain the weak association of histones observed during HSV-1 infection (156). Adenovirus also may not associate with H2AX, ensuring that the local viral response is distinct from the global DDR (53). The core protein VII on incoming adenovirus genome also protects from DDR recognition (134). Although different chromatin states allow viruses to alternate between latent and replication phases of the viral life cycle, chromatinization of incoming naked viral genomes can be detrimental. Deposition of histone variant H3.3 on incoming HSV-1 genomes by the HIRA histone chaperone complex contributes to inhibition of viral gene expression, viral replication, and lytic infection (157) as part of the intrinsic antiviral response of PML bodies. It remains to be seen to what extent the combination of histones and their modifications on viral genomes affects DDR proteins that associate with the viral genome.

6. CONCLUDING REMARKS

Over the past decade, comparisons across viral systems have revealed ways that aspects of the host DNA damage signaling and repair pathways are selectively harnessed or disarmed to facilitate productive viral replication. The examples we have highlighted demonstrate how pathways that ensure faithful replication of the cellular DNA genome can also be exploited for efficient replication of viral DNA genomes, often in noncanonical ways. We mainly focused on signaling pathways that respond to replication stress and DSBs during DNA virus replication, but there are many

other damage and repair pathways that are also manipulated by viruses. In addition, many RNA viruses also induce signaling by kinases in the cellular DDR network (158).

There are intriguing parallels between the pathways that signal DNA damage and those that signal foreign DNA as part of the innate immune response. We have described some of the shared sensors and cross talk between the pathways. Multiple viruses target proteins that function in both pathways, suggesting that identifying common substrates of early viral antagonists will identify key hubs in fundamental cellular networks. Examples already realized to function in this way include components of PML bodies, MRN, and the BRCA1 complex. Viral proteins that mask their DNA genomes from detection in the DDR may also play roles in combatting innate immune signaling. For example, the adenovirus protein VII, which protects incoming viral DNA from DDR activation, also retains the HMGB1 alarmin in cellular chromatin to prevent its release as a danger signal (136). Viral interactions to counter host defenses are a powerful driver of evolution and may contribute to selection pressure in DNA repair proteins. These evolving contact points may contribute to species-specific barriers (159) but may also prevent mammalian DNA repair proteins from functioning effectively.

The associations that have been uncovered between viruses and DDR pathways have a number of therapeutic implications. Since small molecule inhibitors for both DDR- and chromatin-regulated processes have now entered the market as anticancer treatments, these drugs could be repurposed as antivirals or used in targeted approaches against virally induced tumors. Viral proteins that target DDR components could also represent targets for future antivirals. For example, since degradation of TIP60 by HPV E6 is essential to promote survival of HPV-positive cancer cells, conditions that reactivate the acetyltransferase would provide a potential therapeutic avenue to treat patients harboring HPV-positive tumors. Further studies into ways that viruses selectively exploit signaling through DDR kinases and hijack repair proteins for replication will provide insights into fundamental processes and open up opportunities to harness knowledge for therapeutic applications in infectious disease and cancer.

SUMMARY POINTS

1. Virus genomes have limited coding capacity, so infections must have developed ways to harness the cellular DNA replication machinery.
2. During infection and replication, viral DNA genomes must contend with the host machinery of the DNA damage response, which senses viral aberrant nucleic acid structures and replication stress.
3. Viruses activate broad signaling networks through kinases of the cellular DNA damage response.
4. The DNA damage response pathways can be beneficial for virus infection, and cellular factors are recruited to viral replication centers where they facilitate recombination and replication of viral DNA genomes.

FUTURE ISSUES

1. The extent to which the signaling networks activated by virus infection differ from the canonical DNA damage response is unclear.

2. The impact of viral infection on the ability of the host cell to safeguard the integrity of its genome may be selective and thus may prevent accumulation of gross genetic alterations.
3. Proteomic approaches will be helpful by allowing discernment of posttranslational modifications that are induced on cellular replication and repair proteins during infection, as well as the substrates for viral early proteins that disarm host defenses.
4. The cross talk between DNA damage pathways and intrinsic and innate immune recognition is unclear and deserves more attention.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We apologize to groups whose primary research papers could not be cited due to space constraints. We are grateful to past and present members of the Weitzman and Fradet-Turcotte labs and our many collaborators for helpful discussions and contributions to the field. Work on viruses and DNA repair in the Weitzman lab has been supported by grants from the National Institutes of Health (AI067952, CA097093, and AI051686) and funds from the Children's Hospital of Philadelphia. A.F.-T. holds Canada Research Chairs in Molecular Virology and Genomic Instability. Work on viruses and DNA repair in the Fradet-Turcotte lab has been supported by a grant from the Canadian Institutes for Health Research (CIHR 152948), a transition grant from the Cancer Research Society (CRS 19590), and funds from the Foundation J.-Louis Lévesque.

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