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Viral manipulation of DNA repair and cell cycle checkpoints

Mira S. Chaurushiya[1,2] and **Matthew D. Weitzman**[1,*]

[1] Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, CA 92037, USA

[2] Graduate Program, Division of Biology, University of California, San Diego, CA 92093, USA

Abstract

Recognition and repair of DNA damage is critical for maintaining genomic integrity and suppressing tumorigenesis. In eukaryotic cells, the sensing and repair of DNA damage are exquisitely coordinated with cell cycle progression and checkpoints, in order to prevent the propagation of damaged DNA. The carefully maintained cellular response to DNA damage is challenged by viruses, which produce a large amount of exogenous DNA during infection. Viruses also express proteins that perturb cellular DNA repair and cell cycle pathways, promoting tumorigenesis in their quest for cellular domination. This review presents an overview of strategies employed by viruses to manipulate DNA damage responses and cell cycle checkpoints as they commandeer the cell to maximize their own viral replication. Studies of viruses have identified key cellular regulators and revealed insights into molecular mechanisms governing DNA repair, cell cycle checkpoints, and transformation.

Introduction

Cells are equipped with extensive regulatory networks to detect and repair damaged DNA. Activation of DNA damage response (DDR) pathways via signaling from the PI3-kinase-like kinases ATM, ATR, and DNA-PK leads to the phosphorylation of effector proteins that facilitate repair and modulate cell cycle until repair is complete. In the event that damage is irreparable, apoptotic programs are initiated and serve to eliminate the cell, so that deleterious mutations and aberrations are not passed down to daughter cells. Genomic instability is one of the primary hallmarks of cancer and arises from the failure of DNA repair and cell cycle pathways to coordinate the faithful replication of genomic material. Several viruses have been associated with human cancers, and viral proteins implicated in transformation can dysregulate DNA repair and cell cycle pathways. Many viruses have evolved ways to manipulate the same key regulators of these pathways. While some aspects of the cellular DNA damage machinery are activated and exploited by viruses, there is also systematic dismantling of other parts of the cellular signaling network. In this review we focus on the strategies by which viruses perturb these pathways to promote their own replication, and the cellular consequences of their manipulation. Viral oncoproteins provide powerful tools to identify cellular factors crucial to maintenance of genomic integrity. We highlight insights into the basic cellular biology of DNA repair that have been revealed from studying virus interactions, and discuss implications for therapeutic applications.

*Corresponding author E-MAIL weitzman@salk.edu; TEL (858) 453 4100 Ext 2037, FAX (858) 558 7454.

1. VIRAL ONCOGENESIS

Several viruses have been associated with specific human cancers and encode viral oncoproteins that manipulate DNA repair and cell cycle pathways as part of their oncogenic effects [1]. Among these are Epstein-Barr virus (EBV), Human Papillomavirus (HPV), Human T-cell leukemia virus (HTLV-1), Kaposi-sarcoma herpesvirus (KSHV), Hepatitis C virus (HCV), and Hepatitis B virus (HBV) [2]. In many cases oncogenic viruses establish latent or persistent infections that last the lifetime of the individual. Only a small fraction of individuals who harbor these viruses develop cancer, and this usually does not occur until 20–40 years after infection [2]. These trends indicate that the viruses themselves are not sufficient to cause cancer, but that the accumulation of other cellular mutations over time unleashes their oncogenic potential. While the transforming viruses Simian virus 40 (SV40) and Adenovirus (Ad) do not cause human cancers, they are able to immortalize and transform cells in culture via many of the same mechanisms employed by other oncogenic viruses. These viruses therefore provide simple but powerful model systems that offer insights into the molecular mechanisms that govern transformation.

Expression of viral oncoproteins in transgenic mouse models can lead to tumorigenesis. The RNA viruses HCV and HBV, which are associated with hepatocellular carcinoma (HCC), encode core and HBx proteins that transform immortalized cell lines [3]. They can accelerate liver tumors in transgenic mice, with phenotypes that closely resemble characteristics of HBV- and HCV-associated HCC in humans [4,5]. The retrovirus HTLV-1 is associated with adult-T-cell leukemia (ATL) and encodes several putative oncogenes. The most studied HTLV-1 oncoprotein is Tax, which is both necessary and sufficient to transform cells and can cause malignancies when expressed in several tissues [6].

Cellular transformation and tissue specific tumorigenesis can also be accomplished by oncoproteins encoded by the small DNA tumor viruses including HPV-E6/E7, Ad- E1A/E1B, and SV40-Large T antigen (LTag) [7,8]. Transgenic expression of HPV-E6 or -E7 promotes the development of epithelial malignancies [9,10] and when expressed together they induce epithelial and genital carcinomas [11]. The Ad-E1A/E1B proteins induce lung carcinogenesis in transgenic models [12] and SV40-LTag expression can cause malignancies in a variety of tissues [13,14]. In contrast to viruses that encode one or two potent oncoproteins are those that require the combined efforts of several viral proteins to transform cells. For example EBV, which predisposes individuals to various types of lymphomas, requires the functions of LMP1, EBNA1, EBNA2, EBNA3A, EBNA3C, and EBNA-LP to transform primary B cells [15]. Given the links between viral oncoproteins and genome instability, it is not surprising that these viral proteins target many of the same cellular proteins that are mutated in non-virally-induced cancers [16]. Among the pathways most consistently targeted are DNA repair and cell cycle checkpoints, whose manipulation is required for efficient viral replication and whose dysregulation promotes genomic instability, transformation, and tumorigenesis.

2. DNA damage signaling in viral infection

Cells possess several mechanisms to sense and repair different types of DNA damage. Spearheading these pathways are the PI3K-like kinases ATM, ATR, and DNA-PK. ATM is activated at double-stranded breaks (DSBs) whereas ATR responds to single-stranded lesions. DSBs are generated in chromosomal DNA by collapse of replication forks, during programmed rearrangements, by physical stress, and by damaging agents such as ionizing irradiation (IR). These lesions threaten cell viability and can lead to chromosomal translocations and genomic instability. DSBs can be repaired via non-homologous end-joining (NHEJ) or homologous recombination (HR), depending on availability of repair templates and the stage of the cell cycle [17,18]. HR requires functions of the Rad51-family of proteins, while NHEJ is initiated

by association of Ku70/80 proteins with DNA ends and recruitment of the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) [19]. Auto-phosphorylation of DNA-PKcs leads to its release from DNA, allowing processing of the ends for repair via the functions of DNA ligase IV and X-ray repair cross-complementing group (XRCC4).

The Mre11-Rad50-Nbs (MRN) complex is thought to be a sensor for DSBs [20]. The MRN complex is required for efficient activation of ATM, which becomes auto-phosphorylated and then signals to a large number of downstream targets that mediate checkpoints and repair [21]. Among the proteins phosphorylated in the DNA damage cascade are mediators (53BP1 and Mdc1) and effectors (Chk1 and Chk2) of the checkpoint responses. One of the first proteins to be phosphorylated upon DNA damage is the histone variant H2AX, which acts as a signal for recruitment of DNA damage proteins to DSBs [22]. ATR is activated during S phase to regulate origin firing and repair of damaged replication forks [23]. ATR is recruited to single-stranded DNA (ssDNA) at damaged sites through association with ATR-interacting-protein (ATRIP) that recognizes the RPA complex coating ssDNA [23]. The kinase activity of ATR-ATRIP is stimulated by TopBP1 [24]. Upon recruitment, ATR phosphorylates a number of targets including Chk1 for checkpoint activation and RPA32, Smc1, and Rad9 to mediate repair [23]. Many targets of the DNA-PKcs kinase activity have been identified in vitro, although biological relevance is unclear in many cases. Recent studies have demonstrated cross-talk between the PIKKs and shown that there is a complex regulatory network that coordinates NHEJ, HR, and the checkpoint pathways [17,18]. Viral interactions with components of this network are likely to reveal the proteins that regulate specific processes and determine the choice of which pathways are exploited or inactivated (Fig. 1).

2.1. ATM pathways in viral infection

Over the past few years a number of viral examples have demonstrated how ATM signaling during infection can contribute to efficient viral replication. SV40, murine polyomavirus (Py), Herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human cytomegalovirus (HCMV), and EBV all activate ATM and downstream signaling during infection, which is accompanied by recruitment of ATM and other repair proteins to sites of viral replication [25–33]. In some cases, aspects of ATM signaling have been demonstrated to have a benefit for the virus. ATM-mediated phosphorylation of SV40-LTag is detected at the onset of viral replication, and is required for optimal viral DNA synthesis [32]. Inhibition of ATM activity decreases SV40 DNA accumulation [28,32], and delays assembly of viral replication centers and recruitment of cellular DNA repair proteins to these sites [28]. MRN and activated ATM promote HSV-1 replication [29], possibly via their recruitment to viral replication compartments [25,26,29]. DNA damage signaling during HCMV infection is dependent upon ATM, and is also required for efficient virus replication (T. Kowalik, personal communication). It has been suggested that RNA viruses also activate DDR functions that can be beneficial. One recent example is HCV, which replicates better in the presence of ATM and Chk2, and expresses viral proteins that bind ATM and sensitize cells to DNA damage [34,35].

Although these observations demonstrate that ATM-mediated repair pathways can be beneficial for viral replication, many of these viruses also possess mechanisms to inactivate downstream ATM signaling or alter ATM activation as infection progresses. For example, the ICP0 immediate early protein of HSV-1 is an E3 ubiquitin ligase that prevents accumulation of activated repair proteins at sites of cellular DNA damage (Lilley et al., unpublished). It has also been suggested that the MRN complex is degraded at late stages of the SV40 [28] and HSV-1 [36] infection cycles, which could prevent ATM signaling during late stages of virion production or packaging. Although ATM is activated during EBV replication, abrogation of downstream ATM-mediated checkpoint signaling prevents cell cycle arrest and apoptosis [30]. These examples demonstrate how viruses possess mechanisms to modulate ATM

activation at several stages of the pathway and redirect the activities of repair proteins throughout infection.

While viral genome replication can present DNA substrates that activate ATM, some viral proteins can also induce damage responses independently from virus replication. The immediate early protein IE1 of HCMV is sufficient to activate ATM through the E2F-1 transcription factor via Rb inactivation [37]; T. Kowalik, personal communication). Activation of ATM and signaling to downstream substrates such as Chk2 has been reported after expression of SV40-LTag [38], HIV-Vpr [39] and HSV-ICP0 [40] in the absence of virus replication. Although in most cases the mechanism for ATM activation is unknown, nicking of the cellular chromatin has been suggested to induce damage and ATM activation by the Rep proteins of the parvovirus adeno-associated virus (AAV) [41]. Expression of EBV-BGLF4 or its homolog orf36 in murine gamma herpesvirus 68 (MHV68) is also sufficient to induce H2AX phosphorylation [42]. Interestingly, this phosphorylation is primarily a function of the viral kinases themselves but is also augmented by ATM, which together with γH2AX contributes to efficient MHV68 viral replication [42].

During infection with wild-type Ad there is minimal activation of ATM signaling pathways [43,44]. This is because Ad-E4 proteins inactivate the MRN complex early in infection, either via E1b55K/E4orf6-mediated degradation of MRN [43,44] or E4orf3-mediated mislocalization of MRN into nuclear tracks [44–46] and cytoplasmic aggresomes [47,48]. In contrast to wild-type virus, Ad deleted of the E4 region initiates a robust ATM-mediated signaling cascade [43,44]. In addition to preventing ATM-mediated damage signaling, inactivation of MRN promotes Ad DNA replication [46,49,50]. AAV, which uses Ad as a helper and is also limited by cellular damage proteins, benefits from Ad-mediated inactivation of MRN and ATM [51–54]. These different viral systems reveal that the MRN complex is part of the early cellular response to the presence of viral genomes. Degradation of the MRN complex by Ad proteins was also used to demonstrate an upstream function for the MRN complex as a sensor of DNA breaks in mammalian chromosomes [43].

2.2. ATR signaling in viral infection

Although there are many examples of how viruses manipulate the ATM response to damage, much less is known about ATR and virus infections. ATR activation has been observed during infection with HCMV, UV-treated AAV, and E4-deleted Ad [33,43,55]. It has not yet been determined whether this ATR activation is due to viral structures, damage induced at cellular forks, or a combination of lesions. ATR signaling is also activated during infection with the RNA viruses HIV and HBV and this benefits virus replication. HIV-Vpr initiates ATR/Chk1 signaling, perhaps due to HIV-Vpr-induced replication stress, which activates the G2/M checkpoint and promotes HIV infection [56,57]. While HBV-HBx protein initiates ATR signaling that is important for efficient HBV replication [58], it then abrogates downstream ATR-mediated checkpoint signaling [59], and cells expressing HBV-HBx continue through G2/M into mitosis [60]. Thus, similar to EBV manipulation of the ATM pathway, HBV activates ATR damage signaling but then disables downstream ATR-mediated checkpoint signaling.

ATR and its cofactors ATRIP, TopBP1 and RPA all accumulate at Ad replication centers, but ATR signaling is not observed with wild-type virus when MRN is either degraded or localized away from viral centers [43]; CC & MDW, submitted). ATR signaling is activated at late times during infection with some Ad serotypes, and this occurs via E1B-55K association with the cellular factor E1B-AP5 [61]. Some Ad serotypes express E4orf3 proteins that are unable to mislocalize MRN, but these viruses can still degrade MRN via the E1B55K/E4orf6 proteins [62]. The E4orf3 proteins that do not mislocalize MRN cannot prevent ATR activation in response to E4-deleted viruses (CC & MDW, submitted). Together these observations suggest

that the MRN complex is involved in ATR activation, possibly via processing of the viral genome. ATR activation may have a negative impact on Ad infection and may need to be inactivated to promote efficient late protein production (SLS & MDW, unpublished observations). HSV-1 also inhibits ATR activation, and this occurs via HSV-1-ICP0-mediated dissociation of the ATR-ATRIP complex [63]. The observation that HSV-1 activates ATM signaling while inhibiting ATR signaling highlights the ability of viruses to differentially regulate components of the DDR that they may find beneficial versus inhibitory.

2.3. Modulation of DNA-PK and NHEJ by viral proteins

The DNA-PK kinase is modulated by a number of viral proteins, in many cases to prevent processing and end-joining of viral genomes. In the absence of E4 proteins the Ad genome is joined into large concatemers by a process that requires the MRN complex and cellular factors involved in NHEJ [44,64]. The E4 proteins prevent DSB repair and viral genome processing through inactivation of MRN [44] and binding to DNA-PKcs [64]. NHEJ is additionally prevented via dissociation of the DNA ligase IV/XRCC4 complex by Ad-E4orf6 [65] and degradation of DNA ligase IV by Ad-E1B55K/E4orf6 [66]. DNA-PKcs is also targeted by HSV-1, where ICP0 induces its degradation to promote viral replication [67–69]. The role of NHEJ in HSV infection is unclear, with reports showing that depleting Ku70 promotes replication [25] while reducing DNA ligase IV inhibits replication [70]. The HIV-Tat protein causes downregulation of DNA-PKcs expression and thus radiosensitizes cells [71]. HTLV-1-Tax has been suggested to bind DNA-PK and subvert damage signaling [72], which could explain its induction of genomic instability and the requirement for Ku80 [73]. In both cases it remains unclear how these interactions promote viral replication. Some viral proteins are known to be phosphorylated by DNA-PKcs, such as EBNA-LP [74] and SV40-LTag [75], although the biological significance is unknown.

2.4. Viral integration and DNA repair

An obligate step in some viral lifecycles is integration into the host cell genome. Retroviruses undergo reverse transcription to generate linear double-stranded cDNA that becomes integrated into host DNA. Retrovirus integration is mediated by the viral integrase protein, which is sufficient to catalyze DNA breakage and joining reactions [76]. Cellular proteins act as co-factors for integrase catalysis, and are involved in the final step of gap repair [76]. In vitro studies have demonstrated that flap endonuclease and multiple ligases can repair a gapped DNA substrate [77,78]. Cellular proteins have also been implicated in recognition and processing of unintegrated cDNAs. Apoptosis observed after infection of cells deficient for NHEJ factors (DNA-PKcs, Ku86, and XRCC4) was interpreted as failure in repair of integration intermediates [79]. Alternatively apoptosis may result from unintegrated linear viral cDNA during high MOI infections [80], and a number of studies have suggested no role for DNA-PK in viral integration [81,82]. ATM and ATR have also been implicated in HIV integration [83,84], but this is also controversial [81,85]. Other cellular repair factors have been demonstrated to suppress viral infection, including XPB and XPD [86] of the nucleotide excision repair pathway, RAD52 [87], and Rad18 [88]. Metnase is a protein that promotes DSB repair by NHEJ [89] and has been suggested to influence lentivirus integration [90]. Defective repair pathways might indirectly affect virus integration by providing longer lasting breaks that are exploited by viral genomes.

Some viruses do not require integration for viral growth but can integrate their genomes into host chromosomes. One example is AAV, which can be integrated in a targeted manner by the wild-type virus, and in a non-targeted fashion when delivered as a recombinant vector [91]. Host cellular factors have been implicated in processing of the AAV genome [51,52,92,93] and could impact important steps in the virus lifecyle, including genome integration.

3. Viral manipulation of cell cycle and checkpoints

The cell cycle is composed of a tightly regulated sequence of events whose main purpose is to ensure that genomic material is ready to be replicated, faithfully copied, and properly segregated into daughter cells. The integrity of genomic DNA is continually monitored and DNA repair is coordinated with the cell cycle via the G1/S, intra-S phase, and G2/M checkpoints. During mitosis, communication between the mitotic checkpoint complex (MCC) and anaphase-promoting complex/cyclosome (APC/C) ensures the proper alignment and segregation of chromosomes. Viruses manipulate progression through the cell cycle and alter checkpoint signaling in order to provide a favorable environment for their own replication [16] (Fig. 1). In so doing, they can predispose the infected cell to replicate DNA whose fidelity may be compromised and impair the ability of the cell to repair damaged DNA, which together promote genomic instability.

3.1 Cell cycle initiation and G1/S checkpoint

Viruses are streamlined organisms that lack many of the proteins required for genome replication, such as DNA polymerases. They rely on the host cell for these resources, which accumulate during S phase of the cell cycle to replicate cellular DNA. Viral activation of DDR pathways can lead to checkpoint signaling that would stall cell cycle at G1/S. Thus viruses come equipped with mechanisms to initiate cell cycle progression and inactivate G1/S checkpoints to promote S phase transition, despite activation of upstream pathways that would presumably initiate G1/S arrest.

Initiation and progression through the cell cycle is largely orchestrated by the systematic expression and degradation of cyclins, which regulate the kinase activity of distinct members of the cyclin-dependent-kinase (Cdk) family. Progression from G0 to G1 is initiated by exogenous mitogens that stimulate expression of cyclin D. Cyclin D activates Cdk4 and Cdk6 to phosphorylate the retinoblastoma (Rb) protein, resulting in release of the transcription factor E2F from Rb and transcription of target genes, many of which are required for completion of S phase processes [94,95].

Common mechanisms by which viruses initiate cell cycle and activate E2F include promotion of cyclin D activity or dissociation of the Rb/E2F complex in a cyclin-D independent manner. KSHV encodes a cyclin-D type protein, termed v-cyclin, that associates with Cdk6 to phosphorylate Rb [96] and is resistant to Cdk inhibitors [97]. The EBV-EBNA2 and -LP, HTLV-1-Tax, and HBV-HBx proteins upregulate cyclin D in a mitogen-independent manner [98–100] and Tax can also stabilize cyclin D-Cdk4 complexes [101], contributing to Rb hyperphosphorylation and E2F-mediated transcriptional activation. Expression of the full-length HCV genome results in activation of the CDK-Rb-E2F pathway [102] as a result of cooperation between several HCV proteins. The Rb/E2F association itself is consistently targeted via various cyclin-D-independent mechanisms by multiple viral proteins including Ad-E1A [103], HPV-E7 [104], LTag of JCV and SV40 [105], HCMV-IE2 [106], KSHV-LANA [107], EBV-EBNA3C [108,109], HTLV-1-Tax [110], HBV-HBx [111], and HCV-NS5B [112]. Thus distinct viral families have evolved a variety of mechanisms to target the Rb/E2F pathway and promote premature or unscheduled transition into S phase.

Damage sensed via the ATM/ATR pathways results in phosphorylation and activation of Chk2 and/or Chk1, two checkpoint kinases that also phosphorylate downstream targets to initiate G1/S arrest. Chk1/Chk2-mediated phosphorylation of p53 results in upregulation of p21, which functions as a Cdk2 inhibitor. This stalls cell cycle in G1 until damage is repaired and the ATM/ATR-induced repression is lifted. Therefore, in addition to upstream activators, Chk1 and Chk2 are direct targets for viral inactivation of damage responses. HTLV-1-Tax interacts with and inactivates both Chk1 [113] and Chk2 [114], which could contribute to Tax-mediated

abrogation of G1/S checkpoint even in the presence of DNA damage [115]. HBV-HBx inhibits Chk1 activity by preventing ATR-mediated phosphorylation of Chk1 and intra-S phase checkpoint activation after mitomycin C (MMC) treatment [116].

Almost every oncogenic virus possesses mechanisms to manipulate G1/S transition via p53 inactivation, which also serves to prevent apoptosis in infected cells. A selection of the many mechanisms is outlined here. HPV-E6, KSHV-LANA, and Ad-E1B55K/E4orf6 all mediate the ubiquitiation and proteasome-mediated degradation of p53 via recruitment of cellular factors. HPV-E6 recruits the cellular ubiquitin ligase E6AP-100K to degrade p53 [117]. Ad-E1B55K binds p53 to inhibit its transcriptional activity [118], sequesters p53 in cytoplasmic aggresomes [119], and in conjunction with Ad-E4orf6 assembles into a cellular ubiquitin ligase complex composed of Cullin5 and Elongins B/C to target p53 for degradation [120][121]. KSHV-LANA also mediates p53 degradation via coordination of the same components [122]. SV40-LTag association with p53 stabilizes protein levels, but also renders p53 non-functional [123,124]. HBV-HBx represses transcription from the p53 promoter [125], resulting in reduced p53 levels. HTLV-1-Tax has been demonstrated by several groups to inhibit p53-mediated transactivation through a variety of mechanisms [6]. This laundry list of strategies demonstrates the central importance of inactivating p53 functions during virus infections to prevent cell cycle arrest and apoptosis.

In lieu of targeting p53 directly, some viruses transition through the G1/S checkpoint by promoting Cdk2 activity via manipulation of its regulators. Recently HBV-HBx has been shown to interact with cyclin E/A-Cdk2 complexes and destabilize the Cdk2 inhibitor p27, leading to heightened Cdk2 activity [126]. KSHV-v-cyclin can mediate site-specific phosphorylation and inactivation of p27 in certain types of v-cyclin-expressing lymphomas [127]. EBV-infected cells fail to accumulate p21 in response to DNA damaging agents even though p53 expression and damage-induced phosphorylation is unaffected [128]. HBV, while activating ATR and downstream Chk1 phosphorylation, inhibits downstream signaling via degradation of p21, promoting HBV replication [59]. HPV-E7 promotes Cdk2 activity via upregulation of Cdc25A, which is a Cdk2 activator [129]. All of these approaches serve to overcome the G1/S barrier to virus infection.

3.2. S phase and the G2/M checkpoint

In S phase the genome is replicated exactly once to give rise to two complete sets of chromosomes that must then be evenly segregated into daughter cells during mitosis. During S phase, cyclin A functions with Cdk2 to phosphorylate prereplication complexes and ensure that only a single round of DNA replication occurs. Before entering mitosis the cell must pass through several quality control measures to ensure that all DNA is replicated, no damage has occurred during replication, and that exactly two copies of the genome exist [18,130]. Activation of Cdk1 by cyclin B is required for the initiation and completion of mitosis and is the primary target via which the G2/M checkpoint can inhibit mitotic entry. Upon damage or recognition of stalled replication forks, ATM/ATR initiates the phosphorylation cascade from Chk2 to Wee1 to Cdk1, resulting in hyperphosphorylation and inactivation of Cdk1. Chk2 and Chk1 also phosphorylate and inactivate the Cdk1 phosphatase Cdc25c via cytoplasmic sequestration [19].

Many unrelated viruses induce cell cycle arrest in G2 via G2/M checkpoint activation through a variety of mechanisms, and this may serve to maintain the cell in a pseudo S-like state amenable to viral replication [131]. While the mechanisms are distinct, G2/M arrest is achieved by either inactivation of Cdk1 at the G2/M checkpoint and/or interference with mitotic progression. HIV-Vpr has long been known to arrest cells in G2 [132]. Although the mechanisms by which this occurs may be complex, at least one relevant pathway is the activation of ATR via induction of replication stress [133]. HIV-Vpr also functions

downstream of checkpoint pathways by maintaining Cdk1 in its hyperphosphorylated, inactive state via stabilization and promotion of Wee1 kinase activity [134,135] and inhibition of Cdc25c phosphatase activity [136]. Recent work demonstrates that HIV-Vpr coordinates the formation of a ubiquitin ligase complex composed of cellular components DDB1, Cul4A, and a Vpr-binding protein VprBP1 [137,138], which likely serves to mediate the ubiquitination and degradation of a cellular substrate that functions in G2/M transition. Identification of the responsible substrate would therefore provide further insight into G2/M regulation. Vpr highlights the multifaceted ways that viral proteins manipulate key cellular pathways at several points to ensure efficient replication.

Several viruses modulate the activity of the cellular protein phosphatase 2A (PP2A) proteins, including HIV-Vpr [136], Ad-E4orf4 [139], HTLV-1-Tax [140], and SV40-Small T antigen (ST) [141]. It has been shown that PP2A functions as a Cdc25c regulator in G2/M checkpoint activation [142,143] and thus modulation of PP2A may be one of the mechanisms used to initiate G2 arrest. Although HTLV-1-Tax has been shown to initiate G2 arrest in some cell types [114], it also interacts with Chk1 and inactivates Chk1-mediated Cdc25A/C phosphorylation and degradation, resulting in release of the G2/M checkpoint in Tax-expressing cells after nocodazole or IR treatment [113]. EBV-EBNA3C abrogates the G2/M checkpoint [144], which may be accomplished via manipulation of Chk2 signaling [145]. Overall the strategies used by viruses to achieve G2/M arrest are complex and involve a multitude of pathways. The consequences for virus infection also remain obscure in many cases.

3.3 Viral interactions with the MCC and APC/C

Many viruses dysregulate mitosis as revealed by the ability of viral oncoproteins such as HTLV-1-Tax, Ad-E1A, and HPV-E6/E7 to induce centrosome amplification, supernumery centrosomes, and chromosome mis-segregation [146–149]. Proper chromosome segregation depends on coordination of the MCC, which monitors the proper attachment of kinetochores to microtubules, with the APC/C, which regulates entry into anaphase and chromosome segregation, mitotic exit, and subsequent entry into G1 [150]. The MCC is composed of proteins from the BUB and MAD family of genes, which inhibit the APC/C until chromosomes are properly aligned at the metaphase plate. The APC is a ubiquitin ligase complex that regulates the degradation of cell cycle proteins, including cyclins, to ensure timely progression through mitosis [150].

Many viral proteins target MCC components, including MAD and BUB family members, as well as other proteins that mediate kinetochore structure formation during mitosis. HBV-HBx has recently been shown to dysregulate the mitotic checkpoint by targeting BubR1, interfering with the assembly of the MCC at kinetochores and triggering aberrant chromosomal segregation [151]. SV40-LTag targeting of another BUB family member, Bub1, correlates with dysregulated mitotic checkpoint, genome instability and transformation [38,152]. HTLV-1-Tax binding and inactivation of Mad1 helped identify the role of Mad1 in the mitotic checkpoint in humans [153] and evidence suggests that it may also interfere with Bub1 function [154]. EBV infection leads to unscheduled mitotic progression and results in polyploidy and micronucleation [155], which is likely due to EBV-EBNA3C expression [109]. However, the mechanism by which EBNA3C dysregulates the MCC remains to be determined. HSV-1 ICP0 mediates the degradation of centromeric protein C (CENP-C) [156], resulting in kinetochore structure defects and mitotic delay [156].

Viruses can also directly target the APC/C. E2 proteins from high risk strains of HPV can induce genomic instability independent of E6/E7, and this is caused by targeting the APC/C activators Cdc20 and Cdh1 [157]. HCMV inactivates APC/C by dissociating Cdh1 and APC1 from APC/C, and other subunits are redistributed to the cytoplasm as infection progresses

[158]. Thus HCMV uses several mechanisms to ensure that APC/C is inactivated during infection. HTLV-1-Tax binds and activates APC/C, initiating premature entry into mitosis [159] and allowing anaphase progression before chromosomes are properly aligned at the metaphase plate by unscheduled securin degradation [149]. Thus HTLV-1-Tax expressing cells display severe karyotypic abnormalities and cell cycle dysregulation. The Ad-E4orf4 protein also inactivates the APC/C via PP2A targeting [160], which leads to mitotic catastrophe and apoptosis selectively in transformed cells.

4. Implications for therapeutic applications

In addition to highlighting key regulators of cell-cycle progression and DNA repair, understanding interactions between viruses and cellular DNA damage and checkpoint responses provides tools for applications. Cellular repair proteins involved in key steps of the virus lifecycle represent potential targets for antiviral interventions. Viruses can also be developed into agents that selectively replicate and kill tumor cells. Inactivation of DNA damage responses may explain the synergy between these oncolytic viruses and DNA damaging agents, and highlights their potential for overcoming chemoresistance. Finally, viral vectors provide useful tools to study the role of cellular proteins in repair processes.

4.1. Targets for antivirals

Host factors that play essential roles in viral replication offer potential drug targets. In contrast to essential viral proteins, targeting cellular factors precludes problems that arise from drug resistance. Genome-wide studies using RNAi approaches are identifying many host factors required for virus infection, and among these will be DNA repair proteins that may represent attractive drug targets for therapeutic intervention. One example is HIV, where many host factors have recently been identified [161,162]. Although the role of repair factors in HIV infection is controversial [76], it has been suggested that ATM is activated [83,163]. Subsequently it was shown that inhibition of ATM kinase activity with caffeine or a specific small molecule inhibitor can suppress replication of both wild-type and drug resistant HIV-1 [83,164], and can prevent apoptosis of virus-induced syncytia [163]. Inhibition of integration steps mediated by DNA-PKcs [79] could also promote apoptosis and destruction of infected cells.

4.2. Exploiting viruses for cancer therapy and oncolysis

Since there are many viral proteins reported to inactivate aspects of the cellular DNA damage response, they might present an attractive approach for treating tumors that are resistant to current therapies. It has been shown that expression of the adenoviral E4orf6 protein alone can radiosensitize tumor cells [165]. Although the mechanism involved is not defined it may involve binding to DNA-PKcs [64] and is accompanied by prolonged DNA-PKcs auto-phosphorylation [165]. Expression of the ICP0 protein from HSV-1 can also sensitize radioresistant human glioblastoma cell lines, through inhibition of DNA repair and induction of apoptosis [166].

Through deletion of viral genes that are essential in normal cells but dispensable in tumor cells, oncolytic viruses can be generated that selectively replicate in cancer cells [167,168]. Such viruses are promising therapeutic agents for cancer therapy and have undergone extensive testing in the clinic [168]. Emerging data from clinical trials has demonstrated that oncolytic viruses are most efficacious when combined with DNA-damaging agents [169]. Oncolytic adenoviruses have been used in combination with mitomycin C, doxorubicin, cisplatin and 5-fluorouracil. By inactivating host cell responses to DNA damage and preventing repair, oncolytic adenoviruses may overcome chemoresistance [169]. Synergism has also been demonstrated for oncolytic HSV-1 and DNA-damaging agents, where upregulation of DNA

repair genes may enhance oncolysis [169]. Preclinical studies of viral therapy for mesothelioma and malignant glioma using oncolytic HSV-1 have demonstrated enhanced oncolysis by combination therapy with cisplatin, temozolomide, mitomycin C, and irradiation [169]. Although the molecular mechanisms that account for the synergy in combination therapy have not been fully elucidated, it is clear that antitumor efficacy can be augmented by standard chemotherapeutic agents.

4.3. Using viruses for gene targeting

In addition to inadvertent genetic modifications induced by viruses, viral vectors can also be used to introduce targeted alterations into host genes [170]. Vectors based on AAV have proven particularly useful for gene targeting and can be used to generate a range of genetic alterations at remarkably high efficiency [170–172]. Although originally developed for gene correction approaches to gene therapy [173], gene targeting by rAAV vectors can also be exploited to generate knock-in and knock-outs in human somatic cells [174]. rAAV vectors have been used to knockout many genes involved in cancer biology [174], and to generate heterozygous loss-of-function mutations in Ku70 and Ku86 [175]. It has been suggested that gene targeting by rAAV requires cellular factors involved in HR [176]. The explanation for why high targeting rates can be achieved with rAAV vectors is unclear but it may be influenced by the single-stranded nature of the vector DNA, and by cellular factors that bind to the viral genome [53, 170,172]. Various approaches to further improve the gene targeting frequencies obtained with rAAV vectors have been explored. As with other strategies for HR, the frequency of gene targeting can be enhanced by generating DSBs in the target locus [177,178]. Another approach is to decrease random integration events, which can be achieved by impairing the NHEJ pathway [179]. In addition to rAAV vectors, integrase-defective lentiviral vectors have recently been adapted for gene targeting and can achieve high modification rates when combined with DSBs in human cells [180,181].

5. Concluding remarks

Studies of animal viruses have yielded tremendous insights into the dynamic regulation of cell cycle and the process of tumorigenesis. The plethora of strategies developed by viruses to alter DNA repair and cell cycle, indicate that viruses still have much more to teach us about regulation of fundamental cellular mechanisms. The details of how viral oncoproteins dysregulate these pathways and induce transformation are still not fully elucidated. Many cellular proteins involved in replication, gene expression and cell cycle control have historically been found through the viral antigens that interact with them. For example, the important roles played by tumor suppressors p53 and Rb were initially revealed through their association with viral transforming proteins. Recent advances in proteomics and other large-scale high-throughput screens provide broader ways to follow viruses and viral proteins as they hijack cellular pathways. Proteomic analysis of cellular polypeptides that associate with viral replication proteins and intracellular compartments will illuminate ways that viruses accomplish their takeover of cellular functions [25,182,183]. It is likely that future studies will continue to identify novel DNA repair and cell cycle regulators, and these will provide insights into the maintenance of genomic stability and the process of transformation.

One of the most common mechanisms by which viruses target cellular proteins is via ubiquitination. In some cases viruses can encode their own ubiquitin ligases, such as the ICP0 protein of HSV-1. Other viral proteins, such as Ad-E1B55K/E4orf6, KSHV-LANA, HPV-E6, and HIV-Vpr, recruit and redirect cellular ubiquitin ligase complexes to target cellular proteins. By studying viral ubiquitin ligases and their associated complexes we will understand more about the cellular ubiquitin-proteasome machinery and the mechanisms regulating substrate choice and complex assembly. Identifying the cellular targets of these viral ubiquitin ligases will reveal novel key regulators of cellular pathways.

Recent work has uncovered many points of intersection between viruses and the cellular DNA damage machinery. The range of viruses that are recognized by the DNA repair proteins provides an array of unique systems for studying cellular responses. These viruses present a variety of genetic structures to the cell, and deciphering the responses to various viral genomes will contribute to our understanding of how different damaged lesions are recognized and processed by the cell. For example, the Ad genome is joined into concatemers in the absence of the viral E4 genes. However this must involve removal of the virally-encoded terminal protein that is necessary for initiation of viral replication and is thought to protect the termini from nucleases. The Ad genome therefore provides an attractive system to understand the mechanisms used to process protein-bound DNA ends. In turn, the multitude of means by which NHEJ is abrogated by Ad proteins (direct binding, mislocalization, and degradation of necessary cellular factors) highlights the importance of preventing processing of viral genomes. Viral genomes are small and compact, and have evolved to maximize their coding potential. They produce pleitrophic proteins that are optimized for targeting the vulnerable points in the host cell cycle. The use of AdE1b55K/E4orf6 to reveal the role of MRN as a sensor of DSBs in mammalian cells is one example of the value of following viral leads.

Complex networks link pathways and compartments within mammalian cells. Viral proteins that simultaneously target several processes provide attractive ways to elucidate mechanisms governing crosstalk within the network. There are single viral proteins that regulate gene expression, DNA repair, and intrinsic host defenses, linking them to cellular substructures such as PML bodies (ND10) and chromatin. For example, HSV-ICP0 dysregulates ATM-, ATR-, and DNA-PK- mediated DNA repair pathways, alters chromatin structure, and deconstructs ND10 by degrading PML. The Ad-E4orf3 protein also alters gene expression, mislocalizes PML, disrupts DNA repair proteins, and inhibits antiviral responses. Thus these viral proteins are powerful tools to identify cellular targets that function in multiple pathways. Further studies of virus-host interactions will provide insights into basic biological processes that govern recognition and repair of damaged DNA and will help us to understand the consequences of their manipulation during viral replication and cell transformation.

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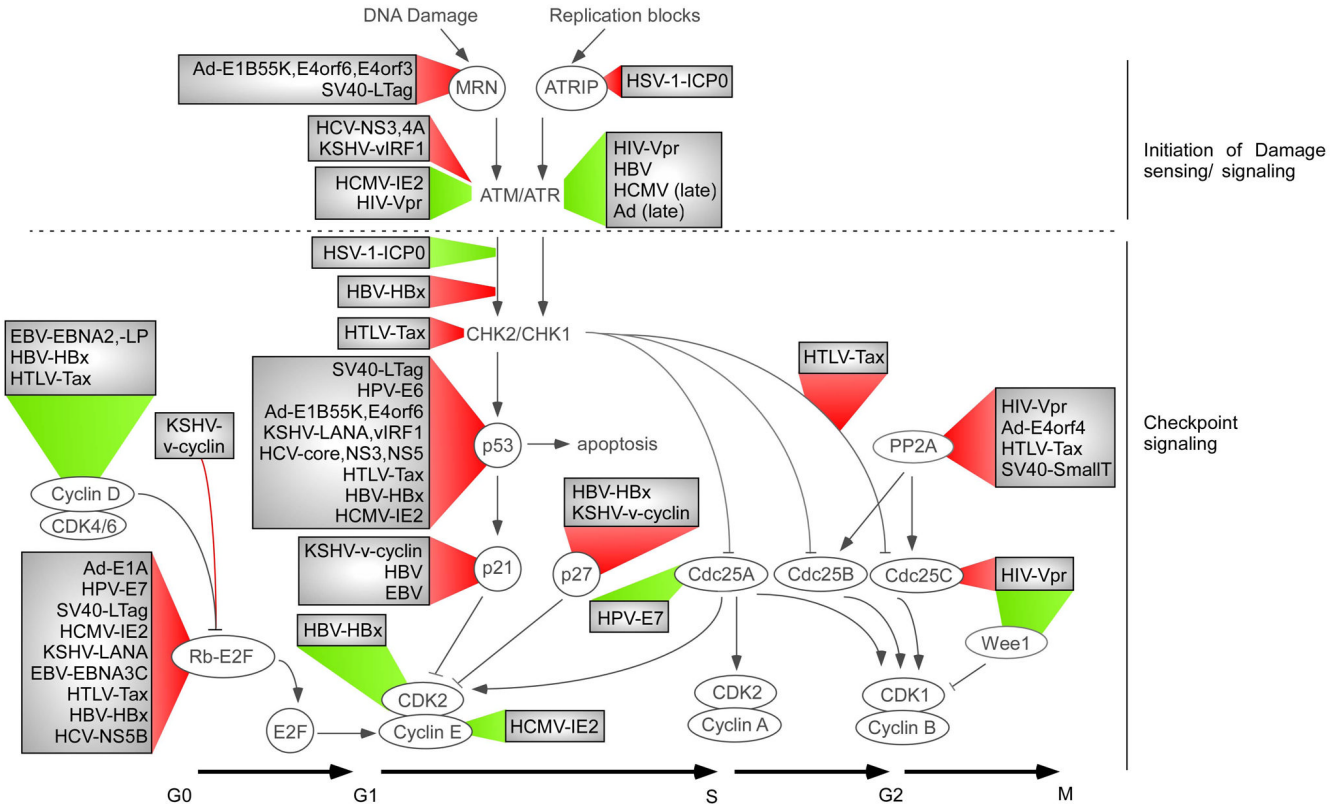

1. .

Viral interactions with ATM/ATR checkpoint pathways and cell cycle regulators. Grey circles and arrows indicate cellular proteins and regulatory networks. Viral proteins boxed in green denote interactions that promote cell cycle progression. Effects of the viral proteins (shaded boxes) on their cellular substrates are indicated by the shaded triangles. Red triangles indicate interactions that are inhibitory to the targeted cellular factors, and green triangles denote interactions that promote activity of the targeted cellular factors. The interactions listed are limited to those covered in this review, and many more viral examples exist that have not been covered here.