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Using or abusing: viruses and the cellular DNA damage response

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During infection, viruses attempt to hijack the cell while the host responds with various defense systems. Traditional defenses include the interferon response and apoptosis, but recent work suggests that this antiviral arsenal also includes the cellular DNA damage response machinery. The observation of interactions between viruses and cellular DNA repair proteins has not only uncovered new complexities of the virus–host interaction but is also reinforcing the view that viruses can reveal key regulators of cellular pathways through the proteins they target.

The cellular DNA damage response

Cellular DNA is constantly under assault from both endogenous and exogenous sources. Maintaining an undamaged genome is a continuous challenge; it has been estimated that each cell must repair over 10 000 DNA lesions per day [1]. Cells have elaborate machinery in place to monitor damage and ensure the fidelity of replication [2,3]. Upon sensing damage, cells initiate signaling pathways that result in activation of checkpoints to prevent replication of damaged DNA. The DNA repair proteins deployed depend on the type of lesion encountered and the phase of the cell cycle.

When the cell detects adducts induced by UV damage, nucleotide excision repair (NER) proteins unwind, nick and re-synthesize the damaged DNA. When the damage is a missing, oxidized or alkylated nucleotide, the base excision repair pathway is responsible for repair. When an incorrect base has been inserted, mismatch repair pathways are activated to correct the mistake. Different kinds of DNA lesions are processed to yield either single or double-stranded breaks. Double-stranded breaks (DSBs) activate the ataxia-telangiectasia mutated (ATM) kinase and its substrates, whereas single-stranded DNA activates checkpoint pathways controlled by the ATM and Rad3-related (ATR) kinase [2,3]. ATR responses are crucial for the cell to respond to replication stress and facilitate replication fork arrest when necessary. DSBs are the most serious type of damage encountered by the cell because there is no complementary sequence to ensure faithful repair. DSBs are induced by endogenous challenges such as immunoglobulin recombination or exogenous insults such as ionizing radiation.

There are two pathways for repairing DSBs in eukaryotic cells: homologous recombination (HR) and non-homologous end joining (NHEJ). The former requires members of the Rad52 epistasis group, whereas NHEJ is a more error-prone repair pathway resulting in religation of DNA ends [3]. The major players in the NHEJ pathway are DNA ligase IV, the X-ray repair cross-complementing group 4 (XRCC4) and DNA-dependent protein kinase (DNA-PK), which consists of a catalytic subunit (DNA-PKcs) and its associated proteins Ku70 and Ku86. Some proteins, such as the Mre11 complex (consisting of Mre11, Rad50 and Nbs1), are involved in both NHEJ and HR. These cellular DNA repair pathways are reviewed elsewhere [3] and are summarized in Figure 1.

Many viruses are now known to interact with the DNA damage sensing and repair machinery (Table 1). These viruses have evolved tactics to eliminate, circumvent or exploit various aspects of the DNA damage response of the host cell. Strategies include activation of repair proteins (Table 1) or targeting of specific cellular factors for degradation or mislocalization (Table 2). This article reviews recent advances in this field and highlights common themes used by viruses in their attempts to commandeer the DNA repair machinery of the host cell.

Viruses and the cellular DNA repair machinery

Recent work has suggested that the cellular DNA repair machinery can recognize viral genetic material as 'damage' [4]. Attempts to process the viral genome could have detrimental results, so some viruses have developed ways to inhibit or circumvent the host-cell response. For other viruses, the cellular response seems to be beneficial, and viruses have evolved ways to hijack cellular DNA repair proteins to aid their own replication.

Viral activation and exploitation of the cellular DNA damage response

Several DNA viruses trigger cellular signaling cascades that are characteristic of a DNA damage response. These include herpes simplex virus (HSV)-1 [5–8], HSV-2 [9], Epstein-Barr virus (EBV) [10], polyomavirus [11] and simian virus 40 (SV40) [12]. The importance of this damage signaling has been investigated using deficient cell lines, RNAi downregulation or specific chemical inhibitors. In the case of HSV-1, polyomavirus and SV40, the DNA damage response was shown to be beneficial because viral replication was less efficient when damage signaling was abrogated [7,11,12]. Preliminary experiments suggest that EBV might be distinct in that the damage response induced by the virus did not aid or inhibit its replication

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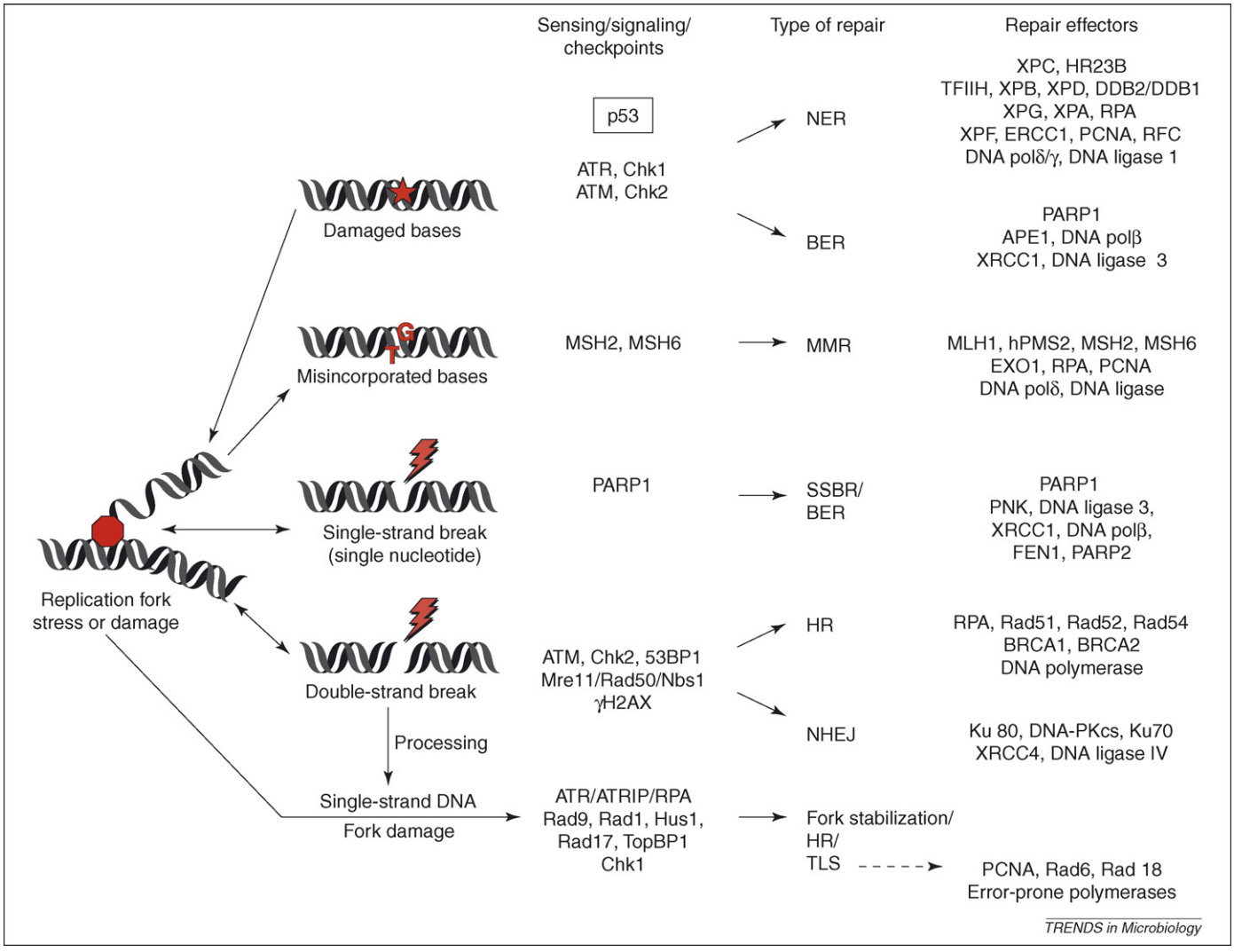

Figure 1. Summary of DNA damage intermediates and repair pathways highlighted in this review. The p53 protein is boxed separately because various types of damage and stress can activate this protein. Replication fork stress can be caused by and/or lead to different types of damage. However, these types of damage also occur independently. The ATM and ATR kinases are involved in numerous types of damage signaling but are not listed in all cases for simplicity. Certain repair pathways (i.e. transcription-coupled repair, single-strand annealing) and proteins are also omitted. Abbreviations: BER, base excision repair; HR, homologous recombination; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end-joining; SSBR, single-strand break repair; TLS, translesion synthesis.

[10]. A unique aspect of the signaling induced by SV40 infection is that the viral T-antigen becomes a substrate for the activated ATM kinase [12]. ATM could also be required to phosphorylate the T-antigen of related viruses [11], suggesting that this might be a general strategy employed by polyomaviruses.

Cellular factors are often recruited into viral replication centers during infection with DNA viruses. Immunofluorescence and proteomic analysis studies of HSV-1 have suggested that DNA repair factors are components of the viral replication centers [7,8,13]. Human cytomegalovirus (HCMV) has also been reported to recruit p53 to sites of viral replication in infected cells [14], and this sequestration might be required for efficient HCMV replication [15]. EBV recruits mismatch repair proteins to viral replication centers and several of these proteins were found to bind to BMRF1, a viral DNA polymerase accessory factor, possibly through its association with the viral genome [16].

Exploitation of the cellular damage response is not limited to DNA viruses. The interactions of retroviruses with the cellular DNA repair machinery has been extensively studied [17]. DNA-PKcs was reported to be required for efficient transduction by retroviral vectors [18]. Subsequently, other PI3-like kinases were also found to be activated following HIV-1 infection [19,20] and might have a role in provirus integration. When caffeine or a small molecule inhibitor was used to block the activity of ATM, HIV transduction and replication were inhibited [19,21,22].

The observation that the DNA damage response benefits the replication of some viruses could have important clinical implications. A small molecule inhibitor of ATM proved efficacious in a proof-of-concept study with HIV-1, even demonstrating antiviral activity against a drug-resistant strain [19]. It will be interesting to see if other pathological viruses will be similarly responsive to DNA repair-based therapies.

The viral triggers that induce DNA damage signaling are still unknown in most cases. Possibilities include incoming or replicating nucleic acid, and virally encoded proteins. In the case of HSV-1, recombination-dependent replication might be the initiating factor [13,23]. In the case of HIV-1, a functional integrase was required for the

Table 1. Viruses that interact with the cellular DNA damage machinery[a]

Virus	Family	Nucleic acid	Genome structure	Signaling pathways		Refs
				Activated	Inhibited	
Herpes simplex viruses 1, 2 (HSV1, 2)	Herpesviridae	DNA	ds, linear	ATM	NHEJ/ATR	[7,8,9,13,38]
Epstein-Barr virus (EBV)	Herpesviridae	DNA	ds, linear	ATM	–	[10]
Human cytomegalovirus (HCMV)	Herpesviridae	DNA	ds, linear	ATM	ATM, ATR	[14,51]
Kaposi's sarcoma herpes virus (KSHV)	Herpesviridae	DNA	ds, linear	–	ATM	[39]
Murine gammaherpesvirus 68 (MHV68)	Herpesviridae	DNA	ds, linear	ATM	ATM	[40]
Adenovirus	Adenoviridae	DNA	ds, linear	–	ATM, ATR, NHEJ	[34,30,35,31,32]
Simian virus 40 (SV40)	Polyomavirinae	DNA	ds, circular	ATM	–	[12]
Polyomavirus	Polyomavirinae	DNA	ds, circular	ATM	–	
JC virus (JCV)	Polyomavirinae	DNA	ds, circular	–	NHEJ	[41]
Human papilloma virus 8, 16 (HPV8, 16)	Papillomavirinae	DNA	ds, circular	–	SSBR	[44]
Adeno-associated virus (AAV)	Parvoviridae	DNA	ss, linear	ATM	–	[29]
Minute virus of mouse (MVM)	Parvoviridae	DNA	ss, linear	–	–	[4]
Hepatitis B virus	Hepadnaviridae	DNA	partially ds, circular	–	NER	[45,47]
Simian virus 5 (SV5) and human parainfluenzavirus 2 (hPIV2)	Paramyxoviridae	RNA	ss, linear	–	–	[46]
Retroviruses	Retroviridae	RNA	ss, linear	–	–	[17,68]
Human immunodeficiency virus 1 (HIV-1)	Retroviridae	RNA	ss, linear	ATM, ATR	–	[17,19,20,24,25,68]
Mimivirus	Mimiviridae	DNA	ds, linear	N/A	N/A	[78]
Omega and Corndog lambda bacteriophages	Bacteriophages	DNA	ds, linear	N/A	N/A	[79]

[a]Abbreviations: ds, double-stranded DNA; ss, single-stranded DNA.

activation of targets downstream of ATM, suggesting that proviral integration could be the trigger [19]. Specific HIV-1 proteins can also trigger cellular damage signaling. For example, the accessory protein Vpr induces cell cycle arrest and phosphorylation of DNA repair proteins [24,25], possibly as a result of cellular replication stress [25]. When ATR kinase activity was impaired, the Vpr-mediated cell cycle arrest was abrogated [20] and a reduction in integration of HIV vector DNA was observed [20,26,27]. In the case of the small adeno-associated virus (AAV), multiple factors elicit a DNA damage response. UV-inactivated viral genomes induced accumulation of repair proteins at virally induced nuclear foci and an ATR-mediated cell cycle arrest [28]. The virally encoded Rep protein might also induce damage by nicking cellular chromatin, arresting cells in S-phase and inducing an ATM-mediated DNA damage response [29].

Viral inhibition of the cellular DNA damage response

For some viruses, the DNA damage response of the host cell is another antiviral obstacle to overcome. Just as viruses have developed ways to block the interferon response and prevent apoptosis, effective counter-attacks against components of the cellular DNA damage response have also evolved (Table 2).

Inactivation strategies employed by viruses usually involve either degradation or mislocalization of repair proteins central to the cellular defense. Adenovirus uses both strategies effectively to prevent the host cell from 'repairing' the viral DNA, an event that would result in covalently linked viral genomes [30]. The adenoviral E4orf3 protein mislocalizes certain DNA repair proteins, such as the Mre11 complex [30–33], while a complex of E4orf6 and E1b55K targets them for proteasome-mediated degradation [30,34]. E4orf3 and E4orf6 also bind to DNA-PK, possibly

Table 2. Examples of specific viral proteins and their cellular targets covered in this review[a]

Virus	Viral protein(s)	Cellular DNA repair proteins targeted			Refs
		Degraded	Mislocalized	Bound	
Adenovirus	E1b55K/E4orf6	Mre11/Rad50/Nbs1, p53	–	DNA-PKcs, p53	[4,30,34,35,53,54]
Adenovirus	E4orf3	–	PML, Mre11/Rad50/Nbs1	DNA-PKcs	[4,31,32,35]
HSV-1	ICP0	DNA-PKcs, PML	ATRIP	–	[36,38,58]
HCMV	Late proteins, possibly pp65 and/or pp71	53BP1(?)	ATM, ATR, Chk1, Chk2	p53	[14,51]
HPV	E6	p53	–	XRCC1	[44,53,54]
HPV	E2	–	–	TopBP1	[42]
KSHV	vIRF1	p53	–	ATM	[39,53,54]
EBV	BMRF-1	–	–	MSH2, MSH3, MSH6, PCNA	[16]
MHV68	M2	–	–	ATM, DDB1, chromatin	[40]
HIV-1	Vpr	–	–	Chromatin	[24,25]
HIV-1	Integrase	–	–	Rad18	[73]
JCV	Agnoprotein	–	Ku70		[41]
SV40	Large T Ag	–	–	Nbs1, p53	[50,53,54]
Hepatitis B	Protein X	–	–	p53, DDB1	[45,47,53,54]
SV5, hPIV2	Protein V	–	–	DDB1	[46]

[a]Dash (–) indicates not fully determined.

limiting viral genome concatemerization [35]. Infection by mutant adenoviruses that are unable to inactivate these DNA repair proteins induces damage responses characterized by activation of both ATM and ATR signaling cascades, and recruitment of many cellular DNA repair proteins to viral replication centers [30,34].

Herpesvirus proteins also inactivate aspects of the cellular DNA damage response. Despite the robust activation of ATM targets during HSV-1 infection, ATR targets are not activated [8,9]. This has been proposed to be a result of mislocalization of the ATR interacting protein ATRIP by the viral IE protein, ICP0 [36]. ICP0 is a key player in the HSV armory against the host cell repair machinery. Disruption by ICP0 of small nuclear domain structures known as ND10 is necessary for efficient viral replication [37], and ICP0 degrades DNA-PKcs, enhancing viral growth [38]. Ku70, another NHEJ protein, also inhibited HSV-1 replication [13]; however, it is currently unclear whether any specific viral proteins counteract this defense. Kaposi's sarcoma herpesvirus (KSHV) and murine gammaherpesvirus 68 (MHV68) are unusual in that they encode proteins (vIRF1 and M2, respectively) that specifically target ATM, presumably to limit the induction of a virus-induced DNA damage signaling cascade [39,40].

Other viruses also encode specific proteins that target DNA damage proteins. For example, the human polyomavirus JCV inhibits NHEJ by encoding a late protein that binds to and mislocalizes Ku70 [41]. The human papillomavirus 16 (HPV-16) E2 binds to TopBP1 and this interaction is required for optimal viral replication [42]. This association is particularly intriguing in light of recent evidence that TopBP1 is required for full activation of ATR [43]. It is tempting to speculate that E2 targets TopBP1 to gain control of the ATR-dependent damage signaling pathway. The E6 protein of HPV-8 binds to the single-stranded DNA break repair factor XRCC1 and this interaction inhibits XRCC1 function [44]. The related UV-induced NER protein DNA damage binding protein 1 (DDB1) interacts with the hepatitis B protein X [45], the MHV68 latency associated protein M2 [40] and proteins from several RNA viruses [46]. The importance of these interactions is still being unraveled but in the case of hepatitis B, this interaction inhibits NER [47], might hypersensitize cells to UV-induced damage [48], and is required for optimal viral replication [49]. Viral proteins whose specific cellular targets are known are listed in Table 2.

Activation and inhibition: viruses with dual responses

Emerging evidence suggests that some viruses first exploit and then inactivate specific cellular DNA repair pathways. The DDB1-containing complex that binds to the MHV68 protein M2 contains ATM and histone proteins [40]. However, M2 is unusual in that it seems to induce ATM activation but then limits its function, preventing the cell from responding to exogenous damage stimuli that might otherwise trigger apoptosis. SV40 infection also activates ATM, and this is required for efficient viral replication [12]. However, it has also been shown that SV40 T-antigen targets Nbs1 to create an environment in which the viral genome can be maximally amplified [50]. It was recently observed that during SV40 infection, T-antigen recruits a cullin-containing ubiquitin ligase to facilitate the degradation of the Mre11 complex (E. Fanning, personal communication).

HCMV can also induce activation of ATM, phosphorylation of H2AX and other downstream targets [14,51]. HCMV seems to recruit certain repair proteins (such as ATM and the Mre11 complex) into viral replication centers [14]. However, HCMV late viral proteins have been suggested to limit the function of some repair proteins by excluding them from viral replication centers [14], mislocalizing them into cytoplasmic aggregates [51] or causing the downregulation of key response elements such as 53BP1 [14]. It has also been shown that blocking ATM and ATR signaling with caffeine enhances viral replication, suggesting that an unabated DNA damage response might be detrimental to HCMV replication [52].

These apparent anomalies imply that categorizing cellular DNA damage responses as either beneficial or harmful for a particular virus might be premature, and suggests that each virus will interact with DNA repair pathways on multiple levels. Future research will reveal how these viruses spatially and/or temporally orchestrate this type of dual response.

Consequences for the cell

Viruses are intracellular parasites, and as such they depend on host cell functions for their replication. Viruses must therefore ensure that the health of the cell is maintained long enough to maximize production of viral progeny.

Cell cycle blocks and checkpoints

Gaining control of the cell cycle is crucial for viral replication. To ensure an abundant supply of nucleotides and other essential replication factors, many viruses override normal checkpoint control and force the cell into S phase. In normal cells, retinoblastoma protein (Rb) binds to the transcription factor E2F to prevent unscheduled S-phase entry. Targeting of Rb is a common strategy used by viruses to promote S-phase (reviewed in Ref. [53]). When a cell experiences DNA damage, checkpoints are initiated to allow time for repair before the damaged DNA is replicated. When viral infection triggers a DNA damage response, the effects on checkpoint control might be synergistic. A virally induced damage response can selectively activate checkpoints, reinforcing maintenance of an S-phase environment. An example of this type of control comes from polyomavirus, in which T-antigen inactivation of Rb promotes S-phase entry. This interaction also induces an ATM-dependent DNA damage response leading to activation of checkpoints, extension of S-phase and increased production of progeny virus [11].

Apoptosis

Viruses have developed a plethora of mechanisms to prevent apoptosis (reviewed in Ref. [54]). These usually include restricting the function of the pro-apoptotic protein p53 (reviewed in Ref. [53]), even though p53 is often activated during infection. Viruses that activate and then limit p53 function include adenovirus, SV40, EBV and

KSHV. HCMV and HSV-1 infections also lead to the stabilization and phosphorylation of p53 [5,6,15], although it is currently unclear exactly how these viruses prevent the pro-apoptotic function.

Another bridge between the DNA damage response and apoptosis is poly(ADP-ribose) polymerase 1 (PARP1). PARP1 has p53-independent roles in modulating histones in response to repairable DNA damage, and roles in promoting apoptosis if the damage is deemed irreparable. PARP1 also binds to single-stranded breaks in DNA where it can help to mediate repair. There is some evidence for an antiviral role for PARP1; it binds directly to EBV and KSHV genomes and its activity negatively correlates with viral replication in KSHV-infected cells [55,56]. Future research is likely to reveal ways in which viruses have evolved to target PARP1.

Viral genomes, ND10 and DNA repair

Several viruses are known to interact with the small subnuclear structures known as promyelocytic leukemia (PML) nuclear bodies or ND10. The interactions between viruses, ND10 and potential links to the DNA damage response are just beginning to be understood. Following infection, the genomes of several DNA viruses localize at ND10. This association seems to be an antiviral response because replication of HSV-1 and HCMV was enhanced in PML knockdown cells, which are deficient in the formation of ND10 [37,57]. Viruses respond to this defense by disrupting ND10 and degrading or mislocalizing key components of these cellular structures (reviewed in Ref. [58]). Several DNA repair proteins are at least partially located at ND10, and it is possible that these structures could function as sensors and processing sites for damaged DNA [59,60]. It is interesting to speculate that one of the reasons certain viruses target ND10 is to gain access to DNA repair proteins.

Transformation and genomic instability

The ability of viral proteins to transform cells has been well documented. Typically, viral gene products are maintained post-transformation but in some circumstances, viral oncogenes are undetectable after the cell has been transformed. An example of such 'hit and run transformation' is that mediated by the adenovirus proteins E4orf3 or E4orf6 in conjunction with E1A [61].

Recent studies have suggested that aberrant, pre-cancerous cell division can trigger the cellular response to DNA damage [62,63]. These studies report that induction of the damage response arrests proliferation or directs the cell towards apoptosis, thereby limiting the malignant progression. Interestingly, the DNA damage response was absent in mature tumors, suggesting that an inactivation of the response might be a contributing factor in the switch between early lesions and cancer. Viral inactivation of the DNA damage response might precipitate this switch and would be a novel mechanism by which these viruses could contribute to cellular transformation.

Multiple links have been identified between papillomaviruses and oncogenic potential (reviewed in Ref. [64]) and these might, in part, involve cellular DNA repair pathways. It has been reported that HPV-16 E7 leads to the phosphorylation of p53, induces γH2AX foci and PARP1 expression, and leads to phosphorylation of cdc2 [65], an inhibitory event that induces cell cycle arrest after DNA damage. In addition to these effects of E7, other HPV factors such as E2 have been reported to have a more general role in virally induced genomic instability: they bind to mitotic chromosomes and induce segregation defects [66]. Other viruses such as HCMV can cause chromosomal breaks and aberrations, which can lead to genomic instability [67]. Viral integration might also have long-term consequences for the host cell. Both retroviruses and rAAV vectors preferentially integrate into actively transcribing genes, thereby affecting transcription patterns (reviewed in Refs [68,69]). In addition, these viral genomes contain unusual DNA structures such as inverted repeats or palindromic sequences that could result in genome instability.

Consequences for the virus

The fate of the virus depends on the cellular environment it encounters upon infection. Many infection events do not result in productive viral replication and this can partly depend on the DNA damage response environment of the host.

Latency and integration

Viruses that establish latency might differentially manipulate the DNA repair machinery to favor lytic replication or latency. For example, HSV-1 is inefficient at inducing a DNA damage response in neurons, the natural site of HSV-1 latency [7]. Because HSV-1 replication is enhanced by the DNA damage response, this deficiency in neurons might stall HSV-1 replication at an early stage and drive the virus into latency. Other herpesviruses might also use the cellular DNA repair machinery to aid in latency establishment or reactivation from latency. For example, the M2 latency protein of MHV68 controls ATM activity to prevent the cell from sensing external DNA damage and inducing apoptosis [40].

Viruses that integrate into the host genome might be susceptible to the DNA damage environment of the cell, especially if they require cellular DNA repair proteins to complete the process. DNA-PKcs activity promotes retroviral transduction, implicating the NHEJ pathway in the sensing or processing of the reverse-transcribed viral cDNA. The excision repair proteins XPB and XPD can degrade retroviral cDNA, resulting in a decrease in viral transduction efficiency [70]. Similarly, Rad52 and Rad18 negatively affect retroviral transduction [71,72] and this might involve the binding of Rad18 to the viral integrase [73]. ATM has also been suggested to promote integration of the HIV-1 provirus [19]. Studies in severe combined immune deficiency (SCID) mice have suggested a role for DNA-PK in inhibiting rAAV integration [74], although interpretation of these results is complicated by an increased level of genome instability, which is known to enhance rAAV integration.

Viral genome processing

DNA repair proteins can also process the genomes of non-integrating viruses. It has been suggested that DNA repair proteins circularize incoming HSV-1 genomes and

that the virus encodes factors to prevent this [75]. However, these data are controversial [76] and challenge the generally accepted model of HSV-1 replication. If adenovirus fails to limit the function of DNA-PKcs, DNA ligase IV and the Mre11 complex, infection results in the formation of viral genome concatemers that are too large to be packaged [30]. Although AAV can integrate, the genome can also persist in an extra-chromosomal form. The unusual terminal hairpin structures of the AAV genome might facilitate its recognition and processing by cellular DNA repair factors [77]. Adenoviral helper proteins E1b55K and E4orf6 could also alter host cell processing of AAV because degradation of the Mre11 complex seems to facilitate wild-type AAV replication and rAAV transduction (R.A. Schwartz *et al.*, unpublished). These studies suggest that the Mre11 complex is an obstacle to parvovirus replication, perhaps as a result of genome processing. In keeping with this hypothesis, there is evidence that several DNA repair proteins, such as those involved in NHEJ, might also limit infection of AAV and related parvoviruses [4].

Evolutionary implications

The potential for viruses to capture cellular DNA repair genes or to evolve repair functions has been explored. The recently identified giant Mimivirus is unusual because it encodes several DNA repair proteins, including Rad2, Rad50, MutS and UV-damage endonuclease homologues [78]. It has also recently been shown that the lambda bacteriophages Omega and Corndog contain Ku homologues and that these cooperate with a DNA ligase from the host cell to facilitate NHEJ, resulting in circularization of the incoming phage genomes [79]. These viruses seem to have captured DNA repair genes from their hosts to aid their own replication. There are already hints in the literature to suggest that this might also be true for mammalian viruses [80] but formal proof awaits future research.

Concluding remarks

The interaction of viruses with the host cell DNA repair machinery is elaborate, and we are just beginning to

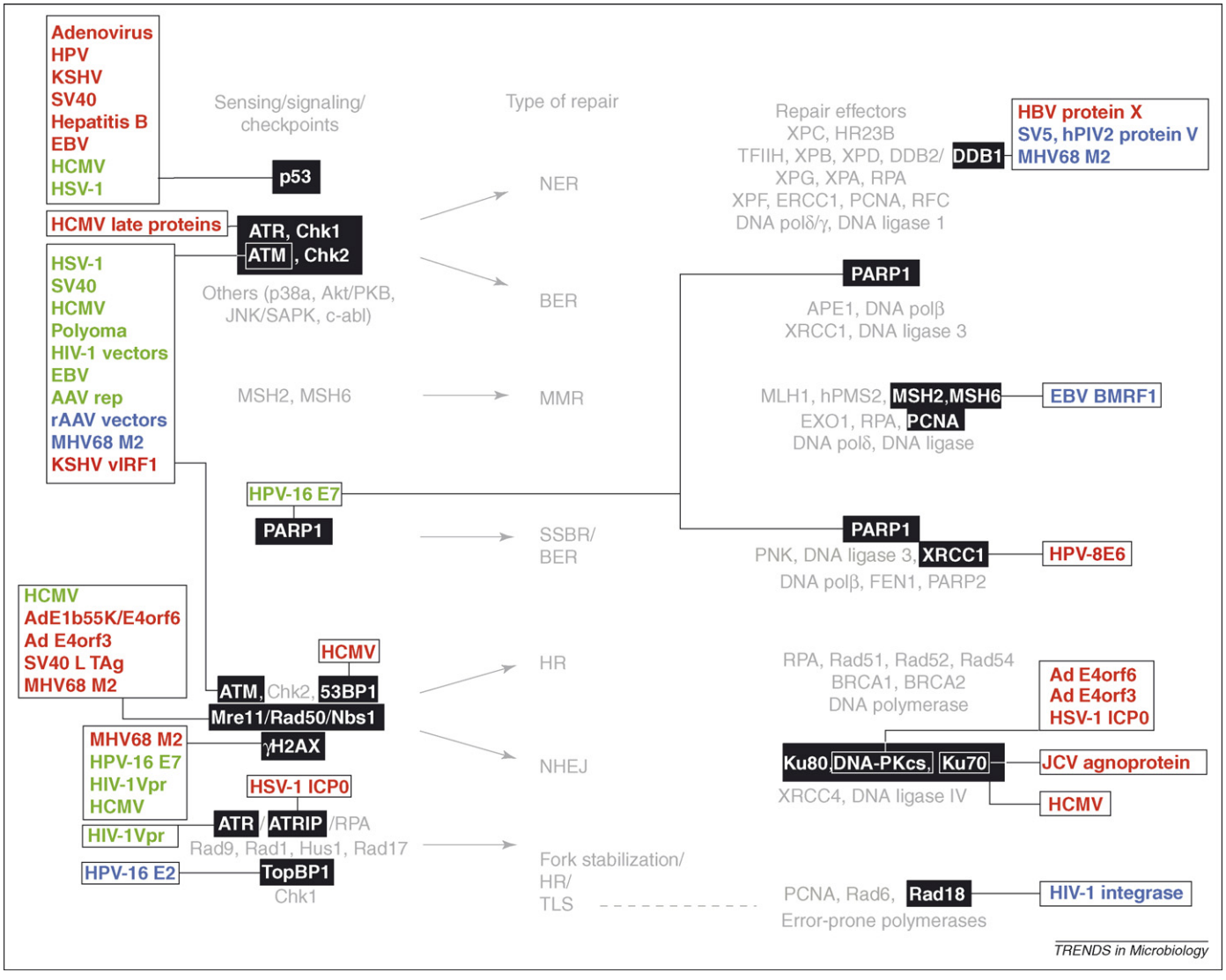

Figure 2. Summary of viruses and viral proteins that target DNA repair pathways. Black boxes highlight the cellular proteins targeted. Viruses and viral proteins that activate cellular damage proteins are shown in green. Viruses and viral proteins that inhibit cellular damage proteins are shown in red. Highlighted in blue are interactions in which the consequence remains to be determined. Although many viruses target p53, only the interactions discussed in this review are shown in the figure. See main text for discussion of interactions between repair proteins and viral DNA. Abbreviations are as stated in the legend to Figure 1.

understand the complexity of the interplay. Figure 2 highlights the cellular DNA repair proteins targeted by the viral factors we have discussed. In general terms, viruses respond to the cellular DNA damage response either by disabling key cellular proteins or activating, recruiting and exploiting host cell factors to aid viral replication. It is likely that virus responses are multifaceted and that individual viruses will interact with the cellular DNA repair machinery on many different levels, inactivating certain aspects while exploiting others. Identifying the cellular proteins targeted by viruses will provide key insights into host responses to both damaged DNA and pathogens.

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