frontiers | Frontiers in Virology

TYPE Mini Review
PUBLISHED 01 May 2024
DOI 10.3389/fviro.2024.1410258

OPEN ACCESS

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RECEIVED 31 March 2024
ACCEPTED 22 April 2024
PUBLISHED 01 May 2024

CITATION
Saladino N and Salamango DJ (2024) Wielding a double-edged sword: viruses exploit host DNA repair systems to facilitate replication while bypassing immune activation.
Front. Virol. 4:1410258.
doi: 10.3389/fviro.2024.1410258

Wielding a double-edged sword: viruses exploit host DNA repair systems to facilitate replication while bypassing immune activation

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Viruses are obligate intracellular pathogens that hijack a myriad of host cell processes to facilitate replication and suppress host antiviral defenses. In its essence, a virus is a segment of foreign nucleic acid that engages host cell machinery to drive viral genome replication, gene transcription, and protein synthesis to generate progeny virions. Because of this, host organisms have developed sophisticated detection systems that activate antiviral defenses following recognition of aberrant nucleic acids. For example, recognition of viral nucleic acids by host DNA repair proteins results in compromised viral genome integrity, induction of antiviral inflammatory programs, cell cycle arrest, and apoptosis. Unsurprisingly, diverse viral families have evolved multiple strategies that fine-tune host DNA repair responses to suppress activation of antiviral defenses while simultaneously hijacking DNA repair proteins to facilitate virus replication. This review summarizes common molecular strategies viruses deploy to exploit host DNA repair mechanisms.

KEYWORDS

antiviral signaling, DNA damage repair, Host-Pathogen Interactions, innate immunity, virus

Introduction

The faithful transmission of genetic information from generation-to-generation is critical for ensuring the survival of an organism. Because genetic material is constantly bombarded by endogenous and exogenous agents, organisms have evolved overlapping repair mechanisms to ensure the stability and accuracy of their genetic code. This process is called the DNA damage response (DDR), which is a highly coordinated network of sensor proteins that detect DNA lesions, kinases that propagate DNA repair signals, and numerous proteins that physically repair damaged DNA. If left unresolved, DNA lesions

can progress to DNA strand breaks that can lead to chromosomal aberrations, genome instability, cell death, and even carcinogenesis.

In general, the DNA lesion itself directly dictates which repair pathway is engaged. Alterations to DNA sequence or structure (at the nucleotide level) are repaired by three main pathways: nucleotide excision repair (NER), base excision repair (BER), or mismatch repair (MMR). These pathways are activated in response to bulky DNA adducts formed due to UV radiation or chemical carcinogens, damaged bases due to spontaneous oxidation, alkylation, or deamination, or mismatched bases due to errors in DNA replication, respectively (1). Interestingly, viruses seldom hijack components of these pathways. One possible explanation is that under normal circumstances viral genomes rarely accumulate damage from these sources given the location of virus replication and the kinetics of how quickly replication occurs. In addition, individual components of these pathways don't directly activate antiviral programs, so their functional state is likely inconsequential to the virus. The best characterized exception to this rule comes from the HIV accessory protein Vpr, as it induces the depletion of several BER and NER proteins through a proteasomal degradation mechanism (2, 3). While the functional relevance of this is debated, it likely serves to counteract the mutagenic potential of host APOBEC3 antiviral enzymes that inflict C-to-U lesions in the HIV genome. Because BER/NER proteins generate abasic sites following the excision of deaminated nucleobases, which can lead to DNA strand breaks, depleting these DNA repair proteins likely preserves HIV genome integrity.

More complex lesions require more intricate processes for repair, as is the case for DNA single-strand breaks (SSBs) and double-strand breaks (DSBs), the latter being most deleterious to a cell (4, 5). Interestingly, viruses most often hijack components of SSB and DSB repair for reasons described in more detail below (Figure 1). The repair of DNA SSBs and DSBs requires a highly coordinated signaling network that is summarized in Figure 1A. ATM (ataxia telangiectasia mutated), ATR (ATM and Rad3-related), and DNA-PK (DNA-dependent protein kinase) are essential players in this pathway and mediate the propagation of repair signals. As is the case for BER/NER/MMR, the DNA lesion dictates which pathway is utilized, with ATR-directed repair being activated upon recognition of SSBs and stalled replication forks, while ATM- and DNA-PK-directed repair pathways are activated by DSBs (6) (Figure 1A). In the case of SSBs and stalled replication forks, replication protein A (RPA) acts as a sensor protein that coats single-stranded DNA and recruits ATR interacting protein (ATRIP) and ATR to the site of damage (7) (Figure 1A). ATR activation requires complex formation with ATRIP and TOPBP1 to trigger catalytic activity and subsequent phosphorylation of downstream targets including H2AX, CHK1, and p53, resulting in cell cycle arrest, chromatin remodeling, and DNA repair (8–11) (Figure 1A).

Canonical DSB repair is mediated by two main pathways, homologous recombination (HR) and non-homologous end joining (NHEJ), with the major difference being the molecular mechanism of repair (Figure 1A). The selection of one repair mechanism over the other is largely dictated by cell cycle phase,

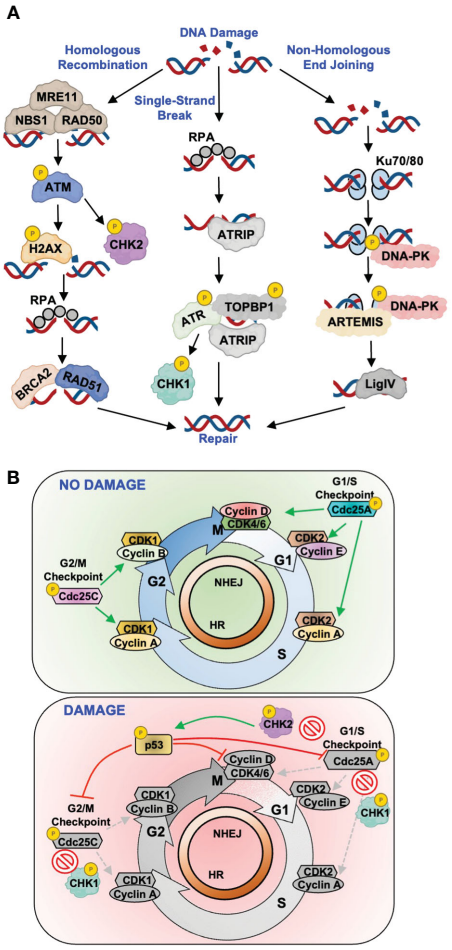

FIGURE 1
Host DNA break repair pathways and examples of virus-directed antagonism. **(A)** Simplified schematic of canonical single-strand and double-strand DNA break repair pathways. Key repair proteins known to be antagonized by viral proteins are depicted for each repair process. **(B)** Depiction of the cell cycle progressing from G1, to S-phase, to G2/M along with the cellular complexes that regulate these transitions. Top: in the absence of DNA damage, Cdc25A/C phosphatases regulate proper progression through the cell cycle by dephosphorylating key Cyclin/CDK complexes to activate their cell cycle regulating functions. Bottom: following the induction of DNA repair signaling, secondary DNA repair kinases CHK1 and CHK2 phosphorylate, and inactivate, Cdc25A/C phosphatases in addition to the p53 regulator.

with HR occurring more frequently during S/G2 whereas NHEJ can occur at all phases (12, 13). In the context of HR, DSBs are sensed by the MRN complex (MRE11, RAD50, and NBS1, Figure 1A). MRN mediates the recruitment and activation of ATM, which phosphorylates and activates key effector proteins H2AX, CHK2, and p53 (14–16) (Figure 1A). This leads to cell cycle arrest and recruitment of downstream repair factors BRCA2 and RAD51 (17, 18) (Figure 1A). In NHEJ, DSBs are sensed by the Ku70/80 heterodimer which recruits the catalytic subunit of DNA-PK to form an active repair complex (19) (Figure 1A). Once NHEJ has been initiated, the Artemis protein processes the broken DNA ends to allow for DNA ligase IV to join the strands and repair the DNA (20) (Figure 1A).

DDR also controls the activation of cell cycle checkpoints, which prevent cells with DNA damage from progressing into mitosis (21). Fine-tuned cell cycle regulation is critical for maintaining proper cell growth and division, and its dysregulation is a hallmark of carcinogenesis (22). There are three major cell cycle checkpoints, G1/S, S-phase, and G2/M, which are regulated by members of the cyclin and cyclin-dependent kinase (CDK) families (Figure 1B, top). Upon the induction of repair pathways, activated CHK1 and CHK2 kinases phosphorylate key cell cycle regulators such as the Cdc25A and Cdc25C phosphatases (Figure 1B, bottom). Phosphorylation of Cdc25A/C inhibits their enzymatic activity to prevent the activation of CDK-cyclin complexes that facilitate progression into the next cell cycle phase. This also prevents dephosphorylation of the tumor suppressor p53, which results in its stabilization and further inhibition of CDK-cyclin complexes (23–25) (Figure 1B, bottom).

In the context of virus infection, DDR proteins can also direct the activation of multiple proinflammatory programs. This is reviewed extensively here (26). During circumstances of abnormal or prolonged DDR signaling, ATM forms a heterodimer with the NF-κB regulator NEMO to trigger NF-κB cytoplasm-to-nucleus translocation and upregulation of proinflammatory cytokines, chemokines, and interferons (27–29). As discussed in more detail below, several viral families induce constitutive DDR signaling to exploit active repair proteins for promoting different phases of virus replication. This prolonged activation of DDR would normally trigger the pro-inflammatory ATM-NEMO-NF-κB nexus; however, many viruses deploy countermeasures to ensure this pathway is disrupted (discussed below). ATM can further mediate the activation of NF-κB signaling by complexing with ELKS, a protein necessary for the activation of the IKK-induced TAK1 kinase (28, 30). Moreover, the cGAS sensor can directly bind cytoplasmic double-stranded DNA to trigger IRF3-mediated transcription of proinflammatory genes through STING activation, in addition to serving as a central control point for integrating inflammatory signals from DNA-PK and MRE11 (31). The cGAS-STING sensor serves as a mechanism to recognize double-stranded DNA viruses that replicated in the cytoplasm, such as poxviruses. Lastly, ATM and ATR can directly bind aberrant DNA structures, such as viral replication intermediates, to trigger DDR responses and proinflammatory signaling (32–34).

Virus-mediated inhibition of host DNA repair

Manipulation of host DDR responses is a broadly conserved activity among diverse RNA and DNA viruses, including adenoviruses (multiple serotypes), herpesviruses [herpes simplex virus-1 (HSV-1), Epstein-Barr virus (EBV), Kaposi's sarcoma herpesvirus (KSHV)], human papilloma viruses (HPV, multiple serotypes), hepatitis viruses [hepatitis B virus (HBV), hepatitis C virus (HCV)], retroviruses [human T-lymphotropic virus-1 (HTLV-1), human immunodeficiency virus-1 (HIV-1)], and rotaviruses (select examples of DDR modulation detailed in Table 1). In general, these viruses deploy one or more proteins that inhibit the initiation or propagation of DDR signaling responses by regulating the activity of primary (ATM, ATR, DNA-PK) or secondary (CHK1 and CHK2) DDR kinases. This establishes an environment favorable for virus replication by inhibiting antiviral programs, maintaining viral genome integrity, inducing cell cycle arrest at phases that permit enhanced viral genome replication and/or gene transcription, and blocking apoptotic responses. In this section, we provide an overview of the molecular mechanisms' viruses use to subvert DDR responses.

Viruses antagonize DDR responses through direct and indirect mechanisms that culminate in the inactivation, depletion, or relocalization/sequestration of key DDR proteins. In many instances, repair factors that initially sense DNA damage or that directly activate DDR signaling pathways, such as the MRN complex, ATM, or DNA-PK, are downregulated transcriptionally or post-translationally. For example, herpesviruses and retroviruses deploy multiple accessory proteins that abrogate DNA-PK or ATM activity to block the initiation of DSB repair signaling, which prevents the activation of innate immune defenses and preserves genome integrity (Table 1). The ICP0 protein of HSV-1 inhibits DSB repair by inducing proteasomal degradation of the DNA-PK catalytic subunit shortly after infection (40, 63) (Table 1). While the mechanistic details are still unclear, DNA-PK restricts HSV-1 replication by affecting genome integrity and activating innate immune defenses such as cGAS-STING (64). Similarly, EBV LMP-1 inhibits DSB repair by downregulating ATM expression *in vitro* and in patient biopsies, which leads to DNA strand breaks, genome instability, and likely contributes to EBV-associated cancers (35, 65, 66). EBV further attenuates ATM-directed signaling by deploying the EBNA3C protein to downregulate H2AX and CHK2 transcripts and proteins, an activity that has been documented in multiple different cell types (36, 37) (Table 1). Collectively, these activities likely serve to disable cell cycle checkpoints and preserve EBV genome integrity.

In addition to antagonizing BER and NER, the HIV Vpr protein induces the depletion of roughly two-dozen cellular proteins involved in DNA repair or DNA modification (67, 68). Vpr achieves this by hijacking a host CUL4-DDB1-containing E3-ubiquitin ligase complex, which normally functions to regulate DNA repair, DNA replication, and chromatin remodeling (69–71) (Table 1). Interestingly, the HBx protein of HBV hijacks the same E3-ubiquitin ligase complex to inhibit DSB repair through degradation of the SMC5/6 repair complex, which enhances HBV transcription (60). Recent evidence indicates that HIV-1 accessory proteins Vpu and Vif can also antagonize DDR through mechanisms distinct, and independent from, Vpr. Vpu utilizes a SUMO E3-ubiquitin ligase complex to inhibit RAD52-mediated non-canonical DSB repair to preserve HIV-1 genome integrity (46) (Table 1). The ends of the double-stranded HIV genome can be recognized as broken DNA and are targeted by either NHEJ or HR for "repair", which generates dead-end circular DNA products. Vpu prevents this while simultaneously suppressing innate immune sensing of the HIV-1 cDNA. Recent work by our group demonstrated that Vif antagonizes cellular phosphatase complexes to inhibit ATM-directed antiviral programs (45) (Table 1). We speculate that this counteracts the constitutive activation of DDR signaling induced by Vpr. For both Vif and

TABLE 1 Summary of virus-DDR antagonism mechanisms and associated functions.

Virus	Protein	Target	Mechanism	Function
EBV	LMP1	ATM	Unknown	Promotes oncogenesis, virus production (35)
	EBNA3C	H2AX	Downregulation of transcription/protein	Blocks anti-proliferative H2AX activities (36)
		CHK2	Destabilizes through direct interaction	Ablates cell cycle checkpoint/progression (37)
	BGLF5	Host DNA	5' to 3' DNA degradation	Activates DDR for viral replication (38)
	EBNA1	Host DNA	Induces ROS production/genome instability	Promotes EBV persistence (39)
HSV	ICP0	DNA-PKcs	Unknown	Delay activation of innate immunity (40)
KSHV	LANA	RAD50, MRE11	Direct or indirect interactions in the cytoplasm	Prevent NFκB activation/antiviral signaling (41)
	ORF57	hTREX	Sequester hTREX leading to R-loop formation	Essential for nuclear export of viral mRNA (42)
HIV	Vpr	UNG, HLTF, SMUG, et al.	Unknown: degradation of repair factors, direct binding to DNA?	Induction of G2/M cell cycle arrest, increased HIV promoter activity and virus production (2, 3, 43, 44)
	Vif	PP2A	Direct binding and proteasomal degradation	Inhibits ATM-directed antiviral programs (45)
	Vpu	RAD52, RanBP	Modulate SUMOylation	Block detection of viral DNA (46)
	IN	Ku70/Ku80	Direct binding to recruit to integration sites	Facilitate viral genome integration (47, 48)
HTLV	Tax	Ku80, DNA-PK	Inhibition of transcription and protein expression	Preserve viral genome integrity (49)
HPV	E6/E7	p53, pRb	Ubiquitination and degradation	Block cell cycle/increase viral replication (50, 51)
	E1	Host DNA	Induction of aberrant replication intermediates and stalled replication forks	Recruitment of DDR proteins to viral replication centers and enhanced viral replication (52)
IAV	M2	PKC, ENaC	M2-mediated ROS production stimulates PKC, decreases ENaC activity	Enhance virus replication (53–55)
AdV	E4orf3	MRE11	Sequester in cytoplasmic aggregates	Prevent recognition of viral genome (56–59)
	E4orf6	TOPBP1, MRE11, DNA ligase IV	Degradation of proteins via viral E3 ubiquitin ligase complex	Prevents viral genome recognition (56–59)
	E1B55K	MRE11, DNA ligase IV	Degradation of proteins via viral E3 ubiquitin ligase complex	Prevents viral genome recognition (56–59)
HBV	HBx	SMC5/6	Degradation through host proteasome	Enhance HBV transcription (60)
HCV	Core	NBS1	Direct binding/inhibition of MRN complex	Prevents viral genome recognition (61)
SARS-CoV-2	ORF6	CHK1	Prevents CHK1 nuclear import, induces deg.	Unknown (62)
	NSP13	CHK1	Prevents CHK1 nuclear import, induces deg.	Unknown (62)
	N	53BP1	Impairs 53BP1 accumulation at DSBs through	Unknown (62)

Representative examples of diverse viral families and their impact on host DNA repair pathways. These examples include viruses that have both single- and double-stranded RNA and DNA genomes.

Vpr, DDR antagonism has been linked to inducing G2/M cell cycle arrest, which has been correlated with increased HIV-1 promoter activity and virus production (43, 44, 72). Another retrovirus, HTLV-1, also targets DSB repair by deploying the Tax accessory protein to diminish DNA-PK activity through downregulation of the Ku80 DNA damage sensor, which is required for recruitment of DNA-PK to DNA strand breaks (49, 73) (Table 1). While the proviral function of this activity has yet to be elucidated, it is likely that this preserves viral genome integrity by preventing NHEJ-mediated circularization of the double-stranded DNA.

Adenoviruses also block DSB repair by inducing the degradation of multiple factors involved in HR or NHEJ. Accessory proteins E4orf3, E4orf6, and E1B55k coordinate to induce E3-ubiquitin ligase-mediated degradation of MRE11, LigIV, and TOPBP1, and can inhibit DNA-PK activity through a direct-binding mechanism (56–59) (Table 1). When functional,

these pathways can recognize and fuse the free adenoviral DNA ends, creating a concatenated byproduct that is defective for replication. Interestingly, antagonizing DNA repair proteins is not constrained to viruses with DNA-based genomes. HCV, which has a positive-stranded RNA genome, utilizes its core protein to directly bind NBS1 and inhibit the formation of the MRN complex (61) (Table 1). In addition, a recent study demonstrated that SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which also has a positive-stranded RNA genome, deploys several viral proteins to inhibit DSB repair by directing the proteasomal degradation of CHK1 and blocking 53BP1 recruitment to sites of DNA damage (62) (Table 1). In these latter two examples, it has yet to be established how viruses with RNA genomes benefit from antagonizing DNA repair pathways.

Another common strategy to modulate DDR responses is the relocalization or sequestration of DNA repair proteins. KSHV utilizes viral factors to recruit RPA and MRE11 to sites of viral DNA synthesis while deploying the LANA protein to relocalize other MRN components to the cytoplasm, thus blocking their ability to activate antiviral inflammatory programs (41, 74) (Table 1). Recruiting DDR proteins to viral replication centers is also a conserved function of HSV-1 and EBV. HSV-1 recruits the ATR/ATRIP complex as well as several MMR proteins to viral replication centers, while EBV recruits ATM and components of the MRN complex (75–78) (Table 1). Recruiting DDR proteins to viral replications centers is also prevalent among adenoviruses, rotaviruses, and HPV. Adenoviruses recruit several proteins involved in ATR-directed repair processes including ATR/ATRIP, RPA, TOPBP1, and multiple RAD proteins to viral replication centers (79, 80). In addition, adenovirus E4orf3 relocalizes MRE11 to nuclear tracts and cytoplasmic aggregates to maintain viral genome integrity during replication (81) (Table 1). In a similar fashion, several HPV serotypes recruit multiple proteins involved in ATM-directed responses, such as H2AX, 53BP1, CHK2, RAD51, and BRCA1 to replication centers (82–84) (Table 1). As was the case above, relocalization of repair factors is not exclusively used by DNA viruses, as rotaviruses, which have a double-stranded RNA genome, utilize viral proteins NSP2 and NSP5 to recruit ATM, CHK2, and the MRN complex to replication centers (85) (Table 1).

Virus-mediated activation of DDR proteins

Viruses have also evolved multiple strategies to activate DDR signaling, which is counterintuitive given the interplay between DDR, antiviral responses, and viral genome integrity discussed above. In some instances, viruses directly damage host DNA to trigger the enzymatic activity of repair proteins, which are then leveraged to facilitate viral genome integration into host chromatin or to promote virus replication. In other cases, viral proteins indirectly antagonize cellular processes that regulate chromatin states or DNA integrity, which inevitably activates DDR proteins. As a bystander effect, these activities often have deleterious consequences for the host cell and can exacerbate pathogenesis. This section highlights the mechanisms deployed by diverse viruses to activate and hijack host DDR responses.

One of best-characterized examples of virus-directed DNA damage is the process of viral genome integration into host chromatin. While this process is traditionally associated with retroviruses, several other viral families including hepadnaviruses, papillomaviruses, and adeno-associated viruses undergo genome integration (86–88). However, it is worth noting that contrary to retroviruses, these latter viruses do not require genome integration for replication. Retroviral genome integration is mediated by the integrase (IN) enzyme, which directly fuses one 5'-end of a viral DNA strand to a corresponding 3'-end of a host DNA strand (89, 90). This results in a SSB for the opposing DNA strand, which is repaired through NHEJ. For many years researchers were puzzled as to why DSB repair proteins would be required for resolving a SSB. This mechanism was clarified following the recent discovery that HIV-1 IN directly binds to the Ku70/80 complex to redirect proteins involved in NHEJ to the site of integration (47, 48) (Table 1).

The natural formation of DSBs during host DNA replication and maintenance can also promote viral genome integration. HBV genomes spontaneously integrate into host chromatin during both chronic and acute infection, which can be enhanced ~10-fold by inducing DSBs in infected liver cells (91) (Table 1). Integrated HBV DNA is often observed in liver tumors and has been correlated with the onset and severity of liver disease and carcinogenesis. Similarly, integration of HPV genomes into host DNA has been correlated with invasive cervical carcinomas. The E6/E7 accessory proteins from high-risk HPV isolates induce host genome instability and spontaneous integration of HPV DNA; however, E6/E7 proteins from low-risk isolates don't exhibit this activity, which potentially rationalizes why high-risk isolates correlate with oncogenesis (50, 51, 92) (Table 1). The HPV E1 helicase further compromises host DNA integrity by inducing aberrant replication intermediates and stalled replication forks (93). This triggers the activation of DDR proteins that are recruited into viral replication centers to facilitate genome amplification (52). Another example of this functional dichotomy is the EBV BGLF5 protein, which is essential for virus replication but also exacerbates carcinogenesis. BGLF5 is a DNase that induces DNA strand breaks to activate DNA repair proteins that are leveraged to facilitate virus replication; however, a consequence of this activity is the induction of genome instability and cellular transformation (38, 94, 95) (Table 1).

Viruses can activate DDR through indirect mechanisms as well. The KSHV ORF57 protein sequesters a host complex required for mRNA processing and stability, which drives a global loss of mRNA stability and the formation of R-loops, DSBs, and the activation of DDR signaling (42). Not only is this interaction essential for efficient export of viral mRNA from the nucleus, but it also contributes to KSHV-associated tumorigenesis (96). In the case of BK polyomaviruses, the process of virus replication itself indirectly activates ATM, ATR, and downstream signaling responses, which are required for optimal virus replication (97) (Table 1). Interestingly, the adenoviral E1A protein is required for facilitating viral genome replication, but as a consequence of its virus-associated activity also induces massive cellular DNA synthesis during S-phase, which triggers significant replication stress and the activation of DDR signaling (98). An additional consequence of these virus-directed

activities is the production of ROS. EBV-encoded EBNA-1 is known to induce host genome instability, DNA damage, and DDR signaling by inducing significant amounts of ROS production (39). EBNA-1-mediated ROS production is thought to promote cellular transformation and the establishment of EBV persistence (39). This is further supported by observations that EBV-mediated B cell immortalization is promoted by oxidative stress and hindered by antioxidants (99, 100) (Table 1). Similarly, influenza A virus (IAV) infection is associated with generating high levels of ROS that contribute to severe pathogenesis (101). ROS are generated as a byproduct of the interaction between the IAV M2 ion channel and mitochondrial membranes (53, 54). Given that M2 modulates epithelial ion channel functions, which are known to influence IAV replication (55), it is likely that M2-generated ROS confers a replication advantage.

Concluding remarks and emerging trends

Future studies investigating the interplay between viruses and host DDR will continue to uncover novel mechanisms used to hijack these pathways and the functional outcomes for virus replication. Importantly, these studies will inevitably yield valuable insights into how host repair pathways function in general and how dysregulation of these pathways leads to human disease. In the last decade alone, research into virus-DDR interactions has led to major discoveries regarding the interconnectedness of DDR and innate immune responses, how virus-mediated subversion of DDR leads to carcinogenesis, and novel facets of DDR and cell cycle regulation. Furthermore, a more comprehensive understanding of virus-DDR interactions can inform the development of therapeutics that exacerbate defects in DNA repair to promote "synthetic lethality" and induce apoptosis of virus-infected or carcinogenic cells (102, 103). Thus, therapeutic interventions that target the virus-DDR nexus could not only suppress virus replication but alleviate the onset and severity of several associated diseases.

Author contributions

NS: Writing – review & editing, Writing – original draft. DS: Writing – review & editing, Funding acquisition, Supervision.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by NIAID R00 award AI147811 (to DS) and startup funds from the University of Texas Health Science Center at San Antonio.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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