

Review Article

NAD⁺-consuming enzymes in immune defense against viral infection

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The COVID-19 pandemic reminds us that in spite of the scientific progress in the past century, there is a lack of general antiviral strategies. In analogy to broad-spectrum antibiotics as antibacterial agents, developing broad spectrum antiviral agents would buy us time for the development of vaccines and treatments for future viral infections. In addition to targeting viral factors, a possible strategy is to understand host immune defense mechanisms and develop methods to boost the antiviral immune response. Here we summarize the role of NAD⁺-consuming enzymes in the immune defense against viral infections, with the hope that a better understanding of this process could help to develop better antiviral therapeutics targeting these enzymes. These NAD⁺-consuming enzymes include PARPs, sirtuins, CD38, and SARM1. Among these, the antiviral function of PARPs is particularly important and will be a focus of this review. Interestingly, NAD⁺ biosynthetic enzymes are also implicated in immune responses. In addition, many viruses, including SARS-CoV-2 contain a macrodomain-containing protein (NSP3 in SARS-CoV-2), which serves to counteract the antiviral function of host PARPs. Therefore, NAD⁺ and NAD⁺-consuming enzymes play crucial roles in immune responses against viral infections and detailed mechanistic understandings in the future will likely facilitate the development of general antiviral strategies.

NAD⁺ or nicotinamide adenine dinucleotide (Figure 1, center) is a co-factor or co-enzyme used in many metabolic reactions. Several enzymes in glycolysis and the Krebs cycle use NAD⁺ to generate NADH. NADH is mainly used in oxidative phosphorylation to generate ATP, during which NADH is oxidized back to NAD⁺. In cancer cells subject to the Warburg effect, NADH is also used to reduce pyruvate to generate NAD⁺ and lactate, making sure that the redox state is optimal for cancer cell proliferation [1]. Thus, NAD⁺ is a vital co-enzyme for cellular metabolism and it is important for cells to maintain proper NAD⁺ levels.

Given the importance of NAD⁺ as a co-enzyme, it is interesting and perhaps surprising that almost all eukaryotes, including mammals, have enzymes that consume NAD⁺ (Figure 1, right). These enzymes can be broadly classified into two categories: enzymes that break down NAD⁺ and transfer the ADP-ribosyl group to other proteins, and enzymes that hydrolyze NAD⁺ to ADP-ribose and nicotinamide.

The first category includes sirtuins, poly-ADP-ribose polymerases (PARPs), and extracellular mono-ADP-ribosyltransferases (ARTs). ARTs are ecto-enzymes catalyzing protein mono-ADP-ribosylation [2]. Their function is relatively little understood and thus will not be further discussed here.

Sirtuins were initially found to be important in gene silencing and calorie restriction-induced life span extension in model organisms [3]. Later studies showed that they couple NAD⁺ degradation to the deacylation (such as deacetylation, desuccinylation, and demyristoylation) [4–7] of various substrates proteins, which mediates the effects of sirtuins in gene silencing and other biological processes, such as regulation of metabolic enzymes and signaling proteins.

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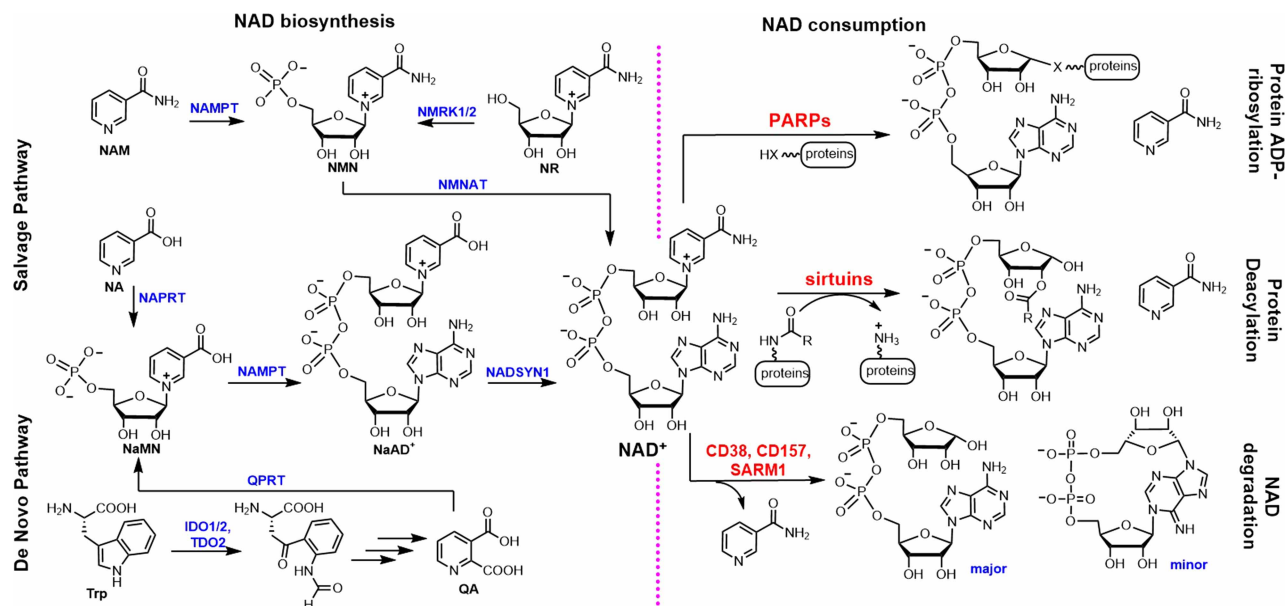


Figure 1. Scheme showing the structure of NAD⁺, NAD⁺-consuming reactions catalyzed by PARPs, sirtuins, and NAD⁺ glycohydrolases, and the NAD⁺ biosynthesis pathways.

Abbreviation for small molecules: NAM, nicotinamide; NA, nicotinic acid; NaMN, nicotinate mononucleotide; NMN, nicotinamide mononucleotide; NaAD⁺, nicotinate adenine dinucleotide; NR, nicotinamide riboside; Trp, tryptophan; QA, quinolinic acid.

PARPs catalyze the addition of ADP-ribosyl groups from NAD⁺ to nucleophilic side-chains of protein, including aspartate, glutamate, serine, cysteine, and lysine [8,9]. Recent studies suggest that they could also ADP-ribosylate DNA and RNA [10]. The PARP family of enzymes, with 17 members in humans, shares a conserved catalytic domain, divided into five subfamilies according to domain structure and function (Figure 2) [11]. Though initially believed to catalyze primarily the transfer of linear or branched poly-ADP-ribose (PAR) or PARylation, recent research showed that many PARPs catalyze mono-ADP-ribosylation (MARylation). PARPs vary in their transcriptional level and cellular localization, and contain a broad range of regulatory domains which allow them to participate in diverse cellular functions [12]. The best-characterized functions involve regulation of stress responses such as DNA damage, apoptosis, and unfolded protein response [13–16]. However, emerging roles in pathogen response and non-stress related regulatory roles have been described [17–22].

The second category of NAD⁺-consuming enzymes include extracellular enzymes CD38 and BST1/CD157, as well as the intracellular sterile alpha and TIR motif containing 1 (SARM1) [23,24]. Although many reports show that they can convert NAD⁺ to cyclic ADP-ribose, the major *in vitro* activity is hydrolysis of NAD⁺ to ADP-ribose and nicotinamide (Figure 1, right) [25,26].

In recent years, it has been increasingly recognized that these NAD⁺-consuming enzymes play important roles in infection and inflammatory response. Below we will briefly review the roles of these NAD⁺-consuming enzymes in viral infection. We focus on the roles of PARPs because a large amount of data supports their vital role in fighting viral infections. Consistent with the role of NAD⁺-consuming enzymes in viral infection, the biosynthesis of NAD⁺ is also regulated during infection and inflammation, which will also be briefly summarized here.

The COVID-19 pandemic, which is still ongoing, reminds us that human society needs general antiviral strategies to fight newly emerging infectious diseases. While there are broad-spectrum antibiotics for treating bacterial infections, there are no general broad-spectrum antiviral strategies. Understanding how our immune system works to fight viral infections may help the development of general antiviral strategies for treating emerging pathogens. Thus, we hope that by understanding how NAD⁺-consuming enzymes help to restrict viruses and how viruses circumvent our immune defenses, we may come out with new broad-spectrum antiviral strategies.

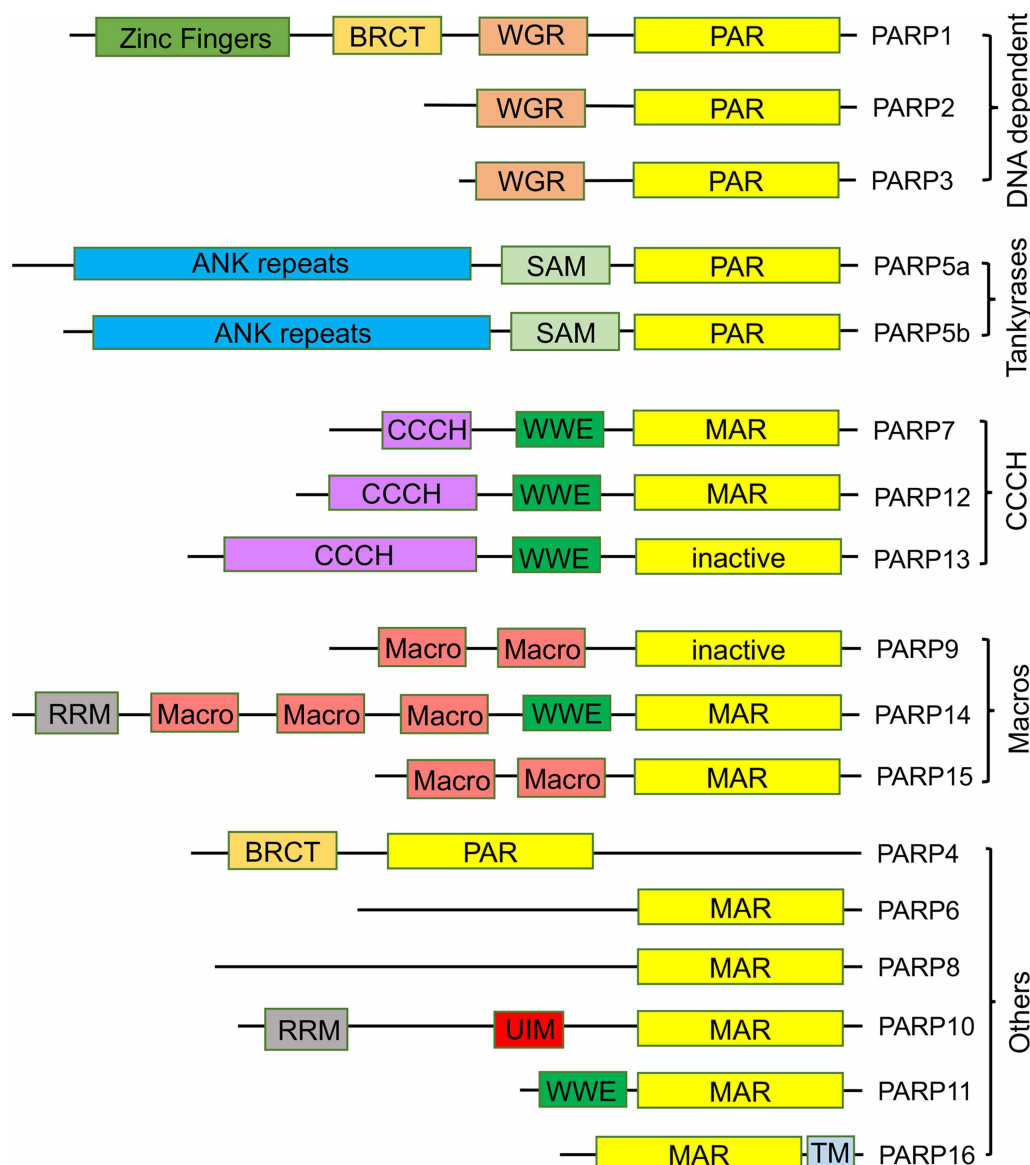


Figure 2. The domain organization of the five subfamilies of PARPs.

The conserved PARP catalytic domain is indicated in yellow. The catalytic domain at the C terminus is conserved in all members and is required for NAD⁺ binding and PARylation activity. The zinc fingers domain in PARP1 is a DNA-binding site. The BRCA1 C terminus (BRCT), ankyrin repeat (ANK), sterile α -motif (SAM), and ubiquitin-interacting motif (UIM) domains are protein–protein interaction modules. The WGR, with conserved W, G and R residues, is a functionally unknown domain. The CCCH domain is a Cys–Cys–Cys–His zinc finger domain. The Macro and WWE (with conserved W, W and E residues) are ADP-ribose binding modules. The RNA recognition motif (RRM) is an RNA-binding motif. TM is a transmembrane domain.

The roles of PARPs in viral infection

The antiviral roles of PARPs are supported by a large body of literature. In fact, one of the PARPs, PARP13, is also named zinc finger CCCH-type antiviral protein 1 (ZC3HAV1) or zinc finger antiviral protein (ZAP). Several other PARP family members are also reported to have antiviral function. Many PARPs are considered interferon-stimulated genes (ISGs), critical for innate immune response. Expression of PARP3, 4, 5a, 5b, and 7-was shown to be induced in cells infected by coronaviruses [22,27,28]. However, conflicting reports about the roles of PARPs in viral infection exist in the literature. Before we provide a more detailed description about the

reported roles of PARPs in viral infection, we will explain a guiding hypothesis that helps us to synthesize the available information.

Our guiding hypothesis is that the PARP family members described below are in general evolved to help fight certain viral infections. However, certain viruses learned to circumvent the antiviral functions of PARPs or even take advantage of their presence to evade the host's immune response and establish successful infections. This is likely the reason why sometimes conflicting reports exist in the literature, with some reporting proviral roles while others reporting antiviral roles for PARPs. In other words, the antiviral roles of PARPs will likely depend on the types of viruses.

The complication could further come from the complexity of the immune system itself. The same biochemical function could serve either as anti-inflammation or pro-inflammation roles, depending on the context. For example, SARM1-catalyzed NAD⁺-degradation generally leads to cell death. If this happens in neurons, it leads to axon degeneration [29]. If SARM1 is activated in immune cells, such as cytotoxic T cells, it will likely promote T cell death [30], which could either promote viral infection or serve to prevent over-inflammation after the infection is taken care of. If this happens in virus-infected cells, the killing of the infected cells may help to limit the spread of the virus, which has been reported in plants [31,32]. Thus, the same biochemical function of SARM1 could lead to different immune outcomes depending on the context. This is an important point to keep in mind when considering the conflicting roles of NAD⁺-consuming enzymes in viral infection.

PARP1

PARP1, which catalyzes PARylation, is the most extensively studied PARP member and inhibitors of PARP1 have been clinically used to treat cancers. The best-understood function of PARP1 is in DNA damage and repair [33]. However, many reports show that PARP1 is relevant for viral infections. The DNA repair function could indirectly contribute to fighting infection as reactive oxygen species (ROS) could induce DNA damage, thus having PARP1 active is important under increased oxidative stress caused by infections.

The role of PARP1 in viral infection depends on the virus (Table 1). For several DNA viruses, including adenovirus, Kaposi sarcoma-associated herpesvirus (KSHV), Epstein–Barr virus (EBV), and hepatitis B virus (HBV), PARP1 is reported to play a protective role. This protective role is mainly due to PARP1 interaction and modification of viral factors.

For example, PARP1-catalyzed PARylation of latency-associated nuclear antigen (LANA) or transcription activator (RTA) protein reduces KSHV infection across two separate studies (Figure 3A,B) [34,35]. PARP1 PARylation combined with phosphorylation of RTA is proposed to reduce RTA binding to viral lytic promoters [31]. Similarly, in adenoviral infection, PARP1 binds adeno-associated virus (AAV) protein Rep to reduce viral genome integration [36].

In EBV infection, PARP1 itself binds a specific lytic promoter (BZLF1), blocking the transition from latency (Figure 3C) [37]. In response to HBV, PARP1 and Ku70/80 form a DNA-binding complex to promote interferon-stimulated genes (Figure 3D) [38]. This highlights a common theme where PARP1 plays several protective roles in the infection, both dependent and independent of its catalytic activity.

These DNA viruses have evolved to counter PARP1-mediated protection via multiple unique mechanisms. To counter PARP1 binding to the EBV lytic promoter, viral protein Zta out-competes PARP1 (Figure 3C). Both murine γ -herpesvirus 68 (MHV-68) and KSHV rely on RTA to promote lytic replication and utilize a processivity factor (PF-8) to bind to and promote degradation of PARP1 [39]. In addition, MHV-68 encodes an open reading frame, ORF49, that binds PARP1 and prevents it from interacting with RTA (Figure 3E) [40].

In contrast with the general protective role in DNA virus infection, the role of PARP1 in RNA virus infection is more complicated. For example, for the HIV-1 retrovirus, many reports indicate that PARP1 promotes HIV infection [41–45]. The pro-viral role is mostly mediated by PARP1's role in the transcription of integrated retroviruses [42,44,46,47]. However, some other studies showed that PARP1 is dispensable for HIV-1 integration, because retroviral replication still can proceed efficiently in PARP1-deficient mouse embryonic fibroblasts (MEFs) [48,49]. PARP1 also decreases interferon alpha/beta receptor (IFNAR) expression upon infection by influenza A virus (IAV) or overexpression of IAV hemagglutinin (HA). Mechanistically, HA interacts with PARP1 and promote its translocation from the nucleus to the cytoplasm, where PARP1 down-regulates IFNAR through proteasomal degradation (Figure 3F) [50]. Additionally, PARP1 can regulate IAV polymerase activity and affects IAV replication [51].

Some reports also indicate a protective role of PARP1 by suppressing HIV-1 gene transcription [46,52]. PARP1 competitively binds to the transactivation response element (TAR) RNA of HIV-1 with Tat/positive

Table 1 Summary of PARP's roles in viral infections

Positive role for host	Ref.	Negative role for host	Ref.
Adeno associated virus (AAV)	[36]	HIV-1	[41–45]
Kaposi sarcoma-associated herpesvirus (KSHV)	[34]	Influenza A virus (IAV)	[50,51]
Epstein–Barr virus (EBV)	[37]		
Hepatitis B virus (HBV)	[38]		
Human immunodeficiency virus 1 (HIV-1)	[46,52]		
Murine leukemia virus (MLV)	[46]		
Murine gammaherpesvirus 68 (MHV-68)	[39,40]		
EBV	[55]	Herpes simplex virus (HSV-1)	[53]
Sindbis virus (SINV)	[61]	Murine coronavirus (MHV)	[62]
Rubella virus	[61]		
Venezuelan equine encephalitis virus (VEEV)	[60]		
Encephalomyocarditis virus (EMCV)	[70]	N/A	
IAV	[71]		
SINV	[71]		
Retrovirus	[71]		
VSV	[71]		
Avian influenza virus (AIV)	[72]	N/A	
Zika virus	[74]	VSV	[73]
		HSV-1	[73]
Vesicular stomatitis virus (VSV)	[78]	N/A	
MHV-68	[78]		
VEEV	[80,82]		
SINV	[80]		
Encephalomyocarditis virus (EMCV)	[80]		
Rift valley fever virus (RVFV)	[80]		
Chikungunya virus (CHIKV)	[80]		
Zika virus	[81]		
MHV	[62]		
Human T cell leukemia type 1 (HTLV-1)	[85]	N/A	
Japanese encephalitis (JE) virus	[86]		
Porcine reproductive and respiratory syndrome virus (PRRS)	[87]		
IAV	[88,89]		
HBV	[89]		
HIV-1	[90]		
MHV-68	[91]		
Alphavirus	[92]		
Newcastle disease virus (NDV)	[98]		
SARS-CoV-2	[103]		
Human CoV-229E	[62]	N/A	
MHV	[62]		

transcription elongation factor b (p-TEFb) complex, leading to p-TEFb displacement from HIV-1 RNA, suppressing Tat-mediated transcriptional elongation [52]. This PARP1-mediated retrovirus transcription inhibition is also efficient against murine leukemia virus (MLV), which is mediated by epigenetic mechanisms that involve DNA methylation and histone deacetylation but independent of the catalytic activity of PARP1 [46]. PARP1 can repress retroviruses prior to viral DNA integration by mechanisms involving histone deacetylases but not viral DNA integration and heterochromatin formation [47].

PARP5a/b

PARP5a and PARP5b, also known as Tankyrases 1 and 2 (TRF1-interacting, ankyrin-related ADP-ribose polymerases) are required for Herpes simplex virus (HSV-1) infection. During HSV-1 infection, PARP5a is phosphorylated via extracellular signal-regulated kinase (ERK), translocates to the nucleus, and co-localizes with infected cell protein 0 (ICP0), an immediate early viral protein that functions as an E3 ubiquitin ligase

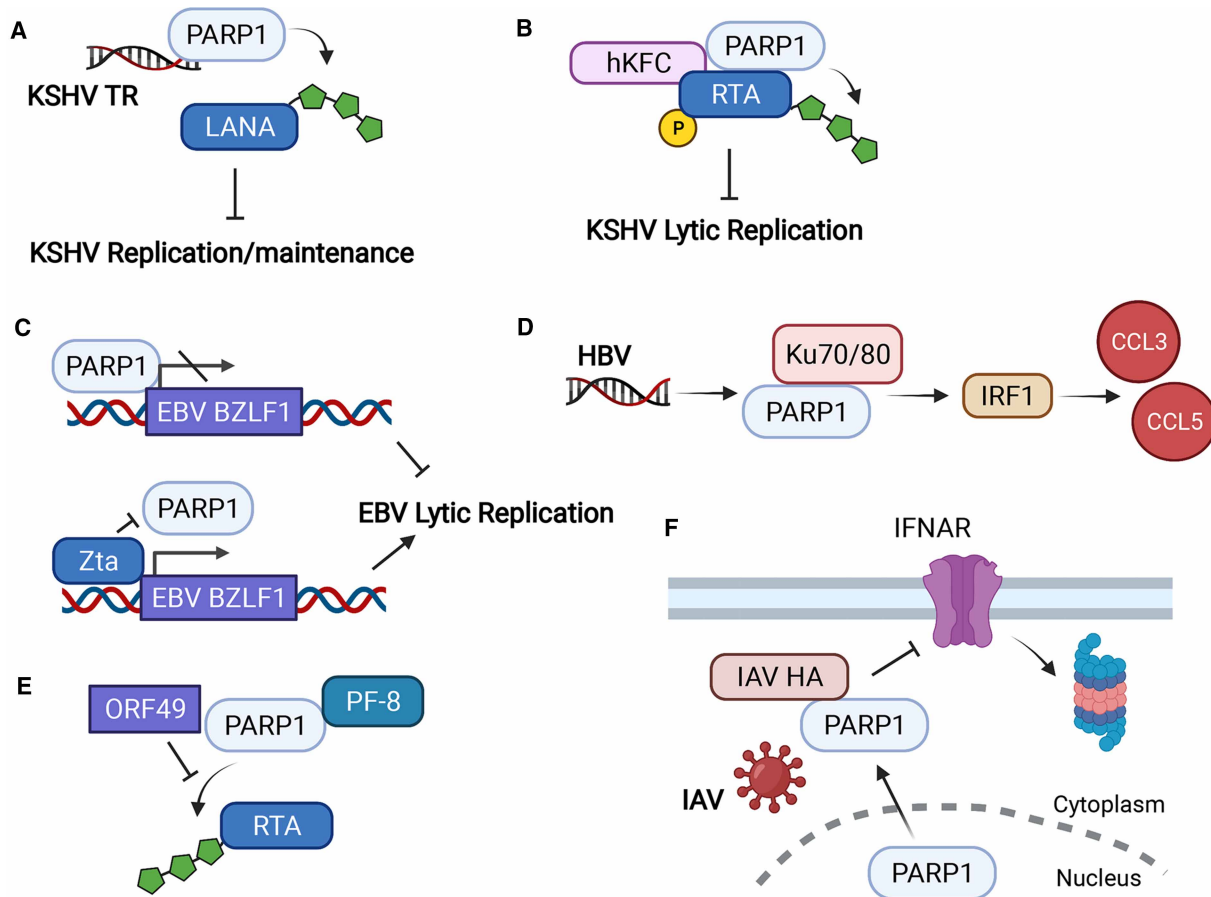


Figure 3. The functions of PARP1 in viral infection.

(A) PARP1 binds to KSHV terminal repeats (TR) and catalyzes the ADP-ribosylation of LANA, reducing KSHV replication in the latency. (B) PARP1 and Ste20-like human kinase homologous to kinases from chicken (hKFC) together bind to and ADP-ribosylate/phosphorylate KSHV RTA protein, which suppresses RTA-mediated KSHV lytic reactivation. (C) PARP1 binds to EBV BZLF1 promoter to prevent its transcription, thus inhibiting EBV lytic reactivation; the viral protein Zta is sufficient to prevent PARP1 binding to the BZLF1 promoter, driving robust BZLF1 expression and lytic reactivation. (D) HBV DNA promotes Ku70/80 and PARP1 to activate interferon regulatory factors (IRFs), which induces chemokine CCL3 and CCL5 levels. (E) ORF49 or PF-8 binds to PARP1, and prevents PARP1 from interacting with RTA, which reduces PARylated RTA and enhances virus replication. (F) Upon IAV infection or overexpression of IAV HA, PARP1 interacts with HA and translocates from the nucleus to cytoplasm, further down-regulating interferon receptor IFNAR through proteasomal degradation. Created with BioRender.com.

(Figure 4A). This leads to proteasome-dependent degradation of PARP5a at the late stage of infection. Knockdown of both PARP5a and PARP5b, or inhibition of their catalytic activity using XAV-939 results in the reduction in viral protein expression and replication [53].

In contrast, in EBV, PARP5 has protective roles. EBV can persist in latency and replicate its genome once per cell division cycle. This replication is dependent on the viral protein EBNA1 binding to its double-stranded DNA at the origin of plasmid (OriP) replication site [54,55]. The EBV OriP structure consists of the family repeats (FR) and a dyad symmetry region. In addition to four EBNA1 binding sites, the dyad symmetry region contains sites (TTAGGGTTA) that bind telomere repeat binding factors TRF1 and TRF2. The factors are important for OriP plasmid maintenance and DNA replication [54]. One study reported that TRF1 binding to telomeric repeats can be regulated by PARP5 [56]. Furthermore, PARP5a/b and TRF2 were identified to interact with the dyad symmetry region in an EBNA1-dependent manner. PARP5 down-regulates OriP replication and plasmid maintenance through PARP activity (Figure 4B) [54,55]. PARP1 can also bind and PARylate EBNA1; its binding to TRF2 induces dyad symmetry structure changes, which impairs EBNA1 DNA binding and functional recruitment of origin recognition complex [57].

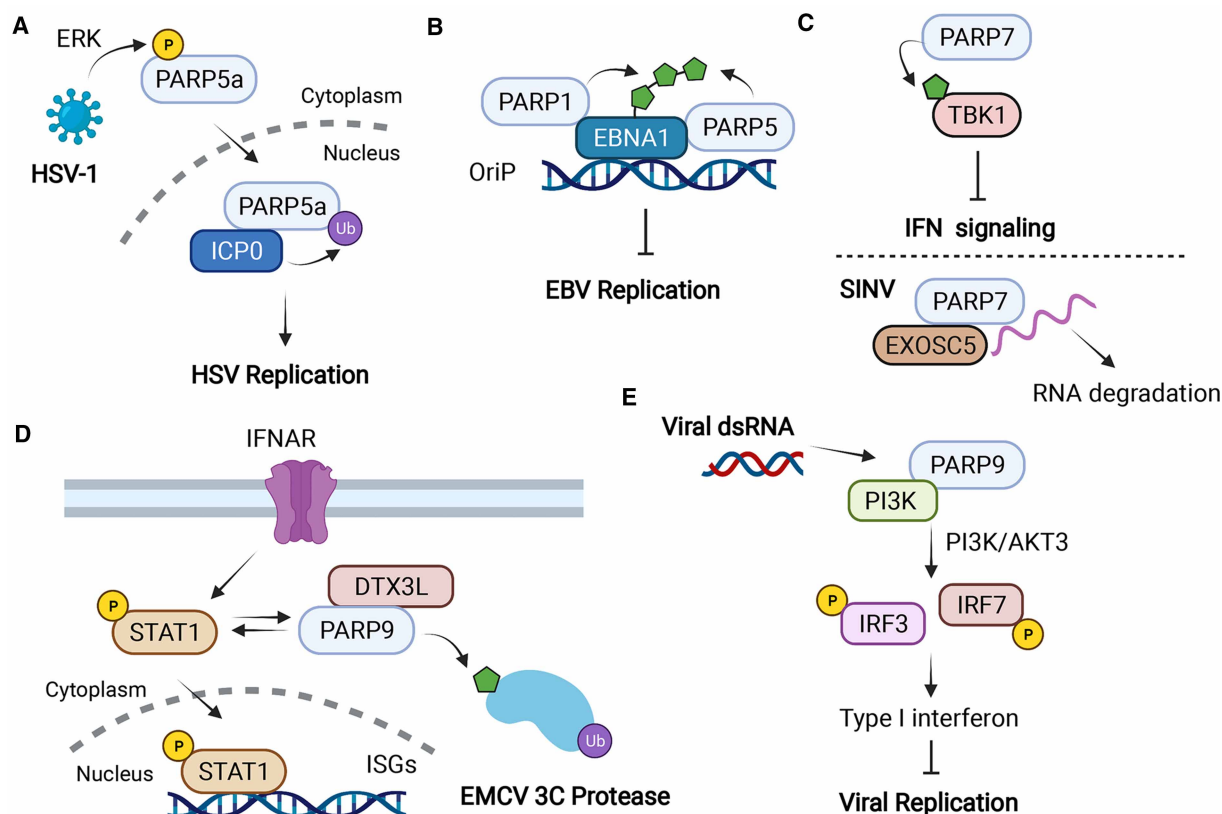


Figure 4. The functions of PARP5a/b, PARP7, and PARP9 in viral infection.

(A) HSV-1 infection induces PARP5a phosphorylation via ERK and promotes its expression and translocation to the nucleus by interacting with ICP0, which results in proteasome-dependent degradation of PARP5a, enhancing HSV replication. (B) PARP1 or PARP5 binds and ADP-ribosylates EBNA1, which inhibits EBV replication. (C) PARP7 mono-ADP-ribosylates TBK1 and down-regulates type I interferon response to viral infection; Upon SINV infection, PARP7 binds viral RNA and EXOSC5 (an exosome component) for RNA degradation. (D) IFN-induced overexpression of STAT1 up-regulates of PARP9 and DTX3L. In turn, PARP9/DTX3L complex binds and promotes STAT1 phosphorylation, nuclear localization, and increases ISGs levels, and triggers degradation of EMCV 3C proteases; (E) PARP9 recognizes viral dsRNA from RNA viruses and employs PI3K/AKT3 pathway to phosphorylate IRF3 and IRF7 for inducing type I IFN, which inhibits the RNA virus infection. Created with BioRender.com.

PARP7

PARP7, or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-inducible PARP (TiPARP), is one of the CCCH zinc finger domains containing PARPs. Unlike PARP1 or PARP5a/b, PARP7 is a mono-ADP-ribosyl transferase. It can bind DNA or RNA and is regulated by aryl hydrocarbon receptor (AHR) [58,59]. PARP7's various functions are tied to its inducible nature, as it can act as a stress response under conditions such as hypoxia [15] or viral infection [60–62]. PARP7 can be induced by a growing list of transcription factors including androgen receptor (AR) [63], estrogen receptor (ER) [64], AHR [59], and HIF-1 α [15]. PARP7 has auto-mono-ADP-ribosylation activity that promotes its own degradation resulting in a half-life estimated to be only 4.5 min [15,65,66]. The unique characteristics of PARP7 gives the ability to quickly modulate a cellular response to viral infection.

The role of PARP7 in viral infection is variable and system dependent. For example, PARP7 is up-regulated after mouse hepatitis virus (MHV) infection in bone-marrow derived macrophages (BMDMs). Knockdown of PARP7 slightly reduces the viral RNA production, which suggests a pro-viral function [62]. AHR signaling down-regulates type I interferon (IFN-1) response to multiple virus types [67]. In this setting, PARP7 mono-ADP ribosylates tank binding kinase (TBK1), a well-known modulator of type I IFN signaling. This ribosylation down-regulates type I IFN response to viral infection by reducing TBK1 S172 phosphorylation (Figure 4C). A recent study found that PARP7 promotes degradation of AHR itself and reduces *Ifnb1*

expression in response to 5'-triphosphate-RNA [68]. Taken together, AHR signaling and PARP7 can be viewed as a 'turn-off' mechanism to avoid deleterious effects of excessive interferon signaling. PARP7 turns off type I IFN response while simultaneously down-regulating the transcription factor (AHR) responsible for this turn-off.

In contrast, PARP7 is reported to have antiviral activity in the *Togaviridae* virus family (positive-strand RNA viruses). PARP7 specifically degrades genomic RNA of Sindbis (SINV) and Rubella viruses in an exosome-dependent manner [57]. Knockdown of PARP7 in U373 human astrocyte cells or knockout of PARP7 in mice leads to enhanced replication of SINV and Rubella virus replication, but it fails to increase replication of other RNA viruses. Thus, the antiviral effect of PARP7 is virus-dependent.

Mechanistically, CCCH-type zinc finger domain-containing proteins regulate RNA degradation and protein translation [69]. PARP7 binds to SINV RNA via its N-terminal CCCH-type zinc-finger domain and induces RNA degradation by recruiting exosome complex component 5 (EXOSC5) (Figure 4C) [61]. In a different study, PARP7, along with PARP10 and PARP12 inhibits a Venezuelan equine encephalitis virus (VEEV) replication model. All three PARPs impact viral replication by blocking protein translation [60], indicating another beneficial role for PARP7 in fighting *Togaviridae* family viruses.

PARP9

PARP9 is catalytically inactive but still mediates antiviral immune response. One study utilized a hyper-efficient STAT1 double-mutant transgenic mouse model to uncover an important role of a PARP9 and Deltex E3 ubiquitin ligase 3L (DTX3L) complex [70]. The STAT1-mutant mice are significantly better at reducing replication of multiple viruses, including encephalomyocarditis virus (EMCV), IAV, and sindbis virus (SINV) but lose efficiency with knockdown of either PARP9 or DTX3L. It is interesting these effects are independent of the PAR-binding function of the PARP9 macrodomains but require the ubiquitination function of the DTX3L-RING domain. The complex interacts with STAT1 and utilizes its E3 ligase activity on histone H2B1 to promote ISG expression (Figure 4D). The complex can also promote degradation of viral EMCV 3C protease. This study highlights PARP9's role in viral response but it is unclear if PARP9 plays a predominant role for wild-type STAT1.

Other reports also connect PARP9 to IFN signaling. PARP9 was recently discovered to be a non-canonical sensor for RNA viruses to promote type I IFN production via the phosphoinositide 3-kinase (PI3K)/AKT3 pathway (Figure 4E) [71]. Knockdown or deletion of PARP9 in dendritic cells, macrophages, or mice inhibits type I IFN production in response to double strand RNA (dsRNA) stimulation or RNA virus infection, including retrovirus, VSV, and IAV. Mechanistically, PARP9 uses its macrodomains for recognizing viral dsRNA, and interacts with PI3K p85 for activating downstream PI3K/AKT3 pathway, independent of mitochondrial antiviral-signaling (MAVS), limiting the RNA virus infection [71].

PARP10

PARP10 is one of the interferon-stimulated PARPs with MARYlation activity. Knockdown of PARP10 increased avian influenza virus (AIV) replication while overexpression of PARP10 reduced AIV [72]. AIV nonstructural protein interacts with PARP10, promotes PARP10 nuclear localization, and reduces endogenous PARP10 expression (Figure 5A), highlighting an interesting countermeasure evolved by AIV. However, this study lacks data in mouse models to more rigorously demonstrate PARP10's antiviral role.

PARP11

PARP11 is the second smallest PARP, with only a single WWE domain and a MARYlation catalytic domain. It is also highly up-regulated by IFN [62]. PARP11 promotes VSV and HSV-1 infection by inhibiting the interferon response [73]. Like PARP1, PARP11 can inhibit IFN signaling by mono-ADP-ribosylating the E3 ubiquitin ligase β -transducin repeat-containing protein (β -TrCP), leading to the ubiquitination and degradation of IFNAR (Figure 5B). PARP11 overexpression restricts the ubiquitin-proteasome degradation of β -TrCP. PARP11 expression is significantly up-regulated during virus infection, including VSV, HSV-1 and IAV. PARP11 knockdown or a pan-PARP inhibitor (rucaparib) treatment limits the replication of VSV and HSV-1. Importantly, the inhibitory effects of rucaparib on viral infection and enhanced ISG expression are largely diminished by PARP11 knockdown. Thus, PARP11 could be a potent regulator of the IFN signaling pathway and antiviral activity [73].

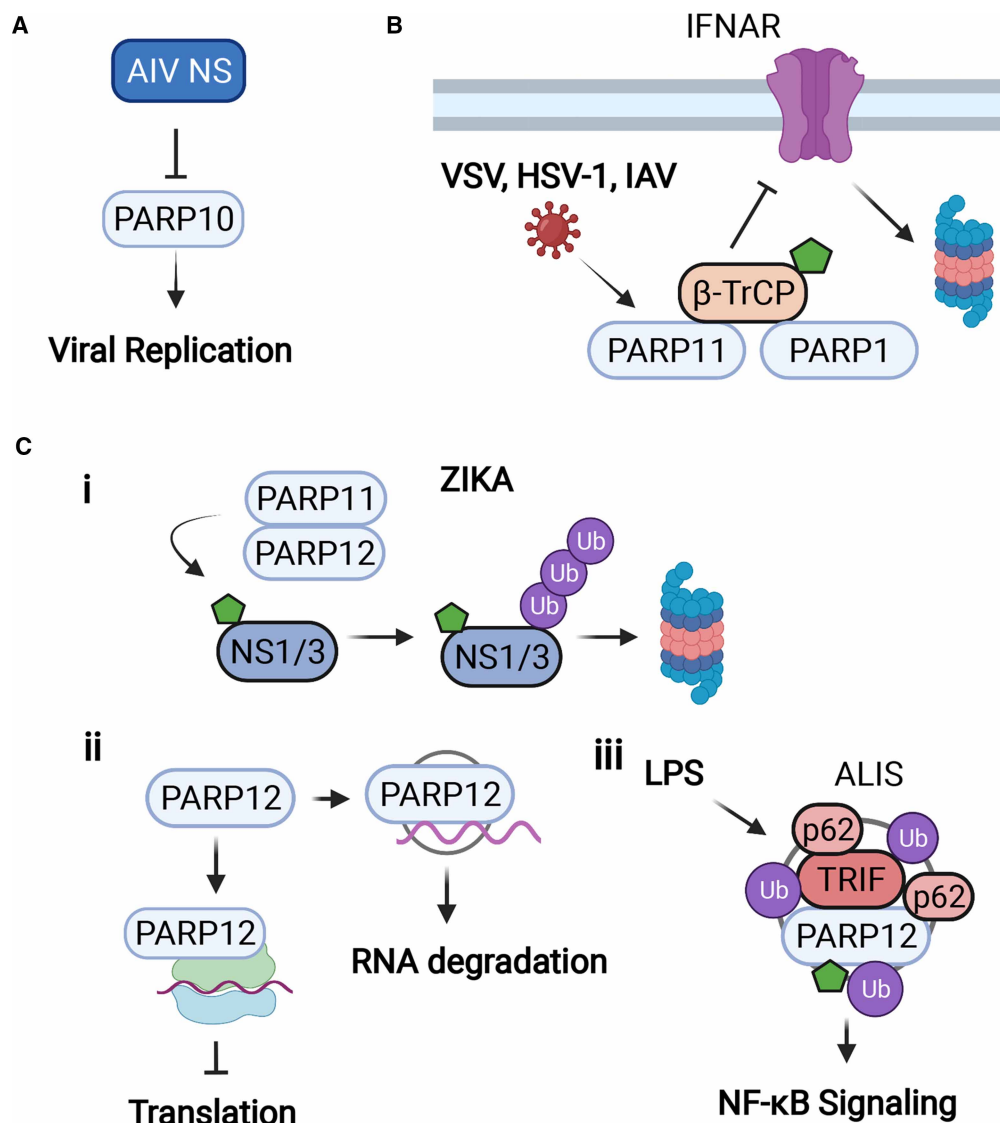


Figure 5. The functions of PARP10, PARP11, and PARP12 in viral infection.

(A) AIV NS binds to and down-regulates PARP10, which enhances virus replication. (B) PARP11 expression is up-regulated during VSV, HSV-1, and IAV virus infections, and PARP11, like PARP1, promotes VSV and HSV-1 infection by mono-ADP-ribosylating β -TrCP, leading to the ubiquitination and degradation of IFNAR. (C) (i) PARP12 expression leads to ADP-ribosylation of Zika proteins NS1 and NS3, leading to their proteasome-mediated degradation, and PARP11 also interacts with PARP12 to enhance Zika virus NS1 and NS3 degradation but independent of its PARP activity; (ii) PARP12 both blocks viral protein translation and binds viral RNA for degradation; (iii) Upon LPS treatment, ALIS structures are positive for PARP12, p62, ubiquitin, and TRIF forms, which regulates NF- κ B signaling. Created with BioRender.com.

In contrast, PARP11 is identified as an anti-Zika virus ISG. It interacts with PARP12 via its WWE domain to enhance Zika virus NS1 and NS3 protein degradation (Figure 5C i) [74]. PARP11 is up-regulated in WT but not IFNAR1^{-/-} cells in response to IFN α / β stimulation and Zika virus infection. Zika virus replication is only suppressed in cells expressing PARP11. Interestingly, PARP11 deletion mutants either lacking the WWE domain or PARP domain do not affect NS1 and NS3 degradation [74].

PARP12

PARP12 is a mono-ADP-ribosyltransferase with four N-terminal CCCH-type zinc-finger domains, a single WWE domain at its center, and a C-terminal PARP catalytic domain. The zinc-finger domains bind both viral

and cytoplasmic RNAs and play important roles in immune cells such as macrophages [69,75–77]. PARP12 is also one of many ISGs [78–80]. The antiviral role of PARP12 was first described in an overexpression screen, where it mildly inhibited the replication of both VSV and MHV-68 [78]. PARP12 was differentially expressed in cells that cleared VEEV replication compared with those that were persistently infected [80]. Further analysis showed that expression of PARP12L, but not PARP12S, restricts VEEV replication, as well as several other viruses including SINV, EMCV, VSV, rift valley fever virus (RVFV), and chikungunya virus. PARP12 also has a role in the restriction of coronavirus replication. PARP12 can restrict MHV replication lacking the ADP-ribosyl-hydrolase (ARH) activity of the coronavirus macrodomain in bone marrow derived macrophage cells [62]. Interestingly, PARP12 was identified in a screen for ISGs that inhibit Zika virus [81]. Using both knockout and overexpression, the authors showed that PARP12 was both necessary and sufficient for the inhibition of Zika virus replication. PARP12 across many virus types and in many systems appears to have a robust protective effect.

The antiviral effect of PARP12 can be achieved through several mechanisms. It can block translation, bind viral RNA at stress granules to promote its degradation [22,80,82], and directly modify viral proteins [28,62,81]. For example, Zika nonstructural proteins NS1 and NS3 are poly-ADP-ribosylated dependent on PARP12 catalytic activity (Figure 5C i). This modification promotes K48-ubiquitination and degradation of these viral components. In contrast with a recent mechanism proposed for PARP7-mediated degradation of HIF-1 α , neither PARP12 WWE domain nor the zinc finger domains are required for this model [15,81]. Notably, the authors further hypothesize that PARP12 mediated PARylation is rate-limiting step prior to the observed PARylated Zika proteins. Although only NS1 and NS3 are reported thus far, it is plausible this mechanism exists for other viral proteins.

In a VEEV infection model, PARP12 (along with PARP7 as previously discussed) is the most effective at reducing viral replication through host translation inhibition [80,82]. Using polysome profiling and mass spectrometry, this study shows that PARP12 exists in two types of complexes: bound to ribosomes and bound to RNA. PARP12 shows cytosolic punctate localization presumably at RNA centers [82], which is dependent on its catalytic activity. PARP12 interaction with RNA is consistent with an RNA interactome of SARS-CoV-2, which identified PARP12 as one of the hits [83]. However, whether the cytosolic stress granule localization contributes to translation inhibition, viral RNA degradation, or multiple mechanisms is not fully understood (Figure 5C ii).

It is documented that endogenous PARP12 in HeLa cells can re-localize into various ‘bodies’ in response to stress [84]. Endogenous PARP12 forms cytosolic bodies after IFN- β or lipopolysaccharide (LPS) treatment termed ‘aggresomes-like structures’ (ALIS) in RAW264.7 immortalized macrophages [82] (Figure 5C iii). The data suggests these structures are sites rich in immune-related proteins such as NF- κ B that may be regulated by PARP12. Overall, PARP12 bodies have several reported roles related to antiviral defense ranging from binding RNA to sites of immune signaling. Understanding the detailed molecular mechanism will help explain PARP12’s critical role in antiviral defense.

PARP13

PARP13, better known as zinc finger antiviral protein (ZAP), is well characterized as an antiviral defense mechanism. Though catalytically inactive, PARP13 has broad-spectrum antiviral activity against human T cell leukemia virus type 1 (HTLV1) [85], Japanese encephalitis virus [86], porcine reproductive and respiratory syndrome (PRRS) virus [87], IAV [88], HBV [89], HIV-1 [90], MHV-68 [91], alphavirus [92,93], and L1 retrotransposition [94]. Given its strong and broad antiviral effects, it is not surprising that several viruses have evolved to counteract PARP13 by degrading PARP13 protein or mRNA [95,96].

In response to both RNA and DNA viruses, ZAP inhibits translation and promotes viral RNA degradation across experimental settings [76,97]. There are four known ZAP isoforms: ZAP extra-long (XL), ZAP-long (L), ZAP-medium (M), and ZAP-short (S). Only ZAPL and ZAPS are highly expressed; thus, their functions are the best characterized. ZAPL contains a PARP domain that is missing key catalytic residues, while ZAPS does not contain the PARP domain. All ZAP isoforms contain two RNA binding domains (RBD), five different zinc finger domains, and two WWE domains. A recent review on ZAP specifically highlights its roles in targeting many different viral families from *Coronaviridae* to *Togaviridae* [97].

ZAPL and ZAPS have remarkably different characteristics. ZAPL is constitutively expressed and acts as an intrinsic antiviral effector, while ZAPS, upon induction by interferon, is a potent stimulator of signaling mediated by the RNA helicase RIG-I during antiviral responses. Mechanistically, ZAPS interaction promotes

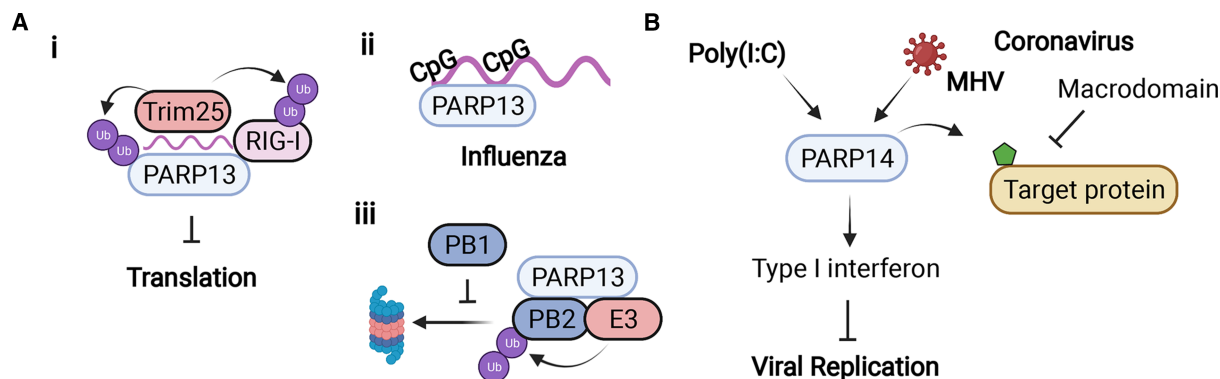


Figure 6. The antiviral functions of PARP13 and PARP14.

(A) (i) PARP13 co-factor Trim25 ubiquitinates both PARP13 and RIG-I to promote antiviral activity; (ii) PARP13 has high affinity for RNA viruses rich in CpG dinucleotides; (iii) PARP13 promotes ubiquitination, and degradation of influenza protein PB2 (and also PA, not shown), which is blocked by competition from influenza protein PB1 for PARP13 binding. (B) PARP14 is required for enhancing IFN production in response to CoV infection (MHV) or poly(I:C) treatment; meanwhile, coronavirus macrodomain prevents the antiviral effect of PARP14 by removing ADP-ribose from target protein. Created with BioRender.com.

RIG-I oligomerization, ATPase activity, and induction of interferon response in response to IAV or Newcastle disease virus [98].

ZAP can help to fight viral infection by binding to viral RNA, which promotes viral RNA degradation and inhibition of mRNA translation. It was originally documented that ZAP binds and destroys specific viral mRNAs as early as 2002 [75,99]. First determined in HIV-1, the ZAP RBDs have a high affinity towards CpG dinucleotides (Figure 6A ii) [97,100]. The field has coined the term ZAP-response element (ZPE) to describe a region of viral coding with high CpG content. Vertebrate genomes have evolved to robustly suppress CpG content and thus lower the frequency of ZPEs. Low CpG-containing viruses, such as HIV-1, are unaffected by ZAP, whereas unnatural additions of CpG to their genomes leads to susceptibility to ZAP expression [100]. It has been shown that ZAP selectively targets multiple spliced viral mRNAs for degradation [90] and inhibits the translation of viral mRNA [101]. The stress granule localization of ZAP is correlated with its antiviral activity [102].

Despite relatively low CpG rates, SARS-CoV-2 viral infection is restricted by ZAPL and ZAPS [103]. This effect is potentiated by the addition of interferons which induces more ZAP, among other PARP family members [62,103]. ZAP, along with Trim25 and PARP12 (discussed in the PARP12 section and below), directly bind SARS-CoV-2 RNA [83]. To counter ZAP targeting, SARS-CoV-2 shows evidence of CpG suppression over the course of a 5-month study [104]. Furthermore, phylogenetic mutation analysis suggests that C and G mutations are reflective of SARS-CoV-2's attempts to counter host defense systems such as ZAP targeting [105].

Like other PARP family members, ZAP plays additional roles in degradation of viral RNA or proteins. Specifically, ZAP recruits host cofactors, such as E3 ubiquitin ligase, Trim25, to target and destroy viral DNA or RNA. This enzyme can ubiquitinate ZAP itself, bind RNA, and improve ZAP antiviral activity across multiple studies (Figure 6A i) [97,103]. After binding, ZAP-mediated degradation proceeds via complicated mechanisms involving exoribonuclease complexes and RNA helicases to unwrap and degrade RNA [97].

ZAPL can also exert antiviral activity by promoting the degradation of viral proteins. For IAV, ZAPL binds the viral PB2 and PA polymerase proteins, leading to their proteasomal degradation (Figure 6A iii). After the PB2 and PA proteins are ADP-ribosylated, they are associated with the region of ZAPL that includes both the PARP domain and the adjacent WWE domain that is known to bind ADP-ribose. These complex proteins are then ubiquitinated, followed by proteasomal degradation. This antiviral activity is counteracted by the viral PB1 polymerase protein, which binds close to the PARP domain and causes PB2 and PA to dissociate from ZAPL and escape degradation. This could explain why ZAPL only moderately inhibits IAV replication. Eliminating PB1 binding to ZAPL would substantially increase the inhibition of IAV replication, so that the PB1 interface with ZAPL is a potential target for antiviral development [88].

ZAP also has additional antiviral roles beyond regulating viral RNA or protein degradation. For example, ZAP can directly bind host RNAs and specifically regulate their translation to tune the immune response. Specifically, ZAP can decrease TRAILR4 translation and can modulate TRAIL-regulated apoptosis [106]. Some reports indicate ZAP may either repress or promote IFN response gene translation via different mechanisms. More interestingly, there are reports that under some viral infections such as HIV-1, RNAi activity is turned down directly after infection and this promotes IFN response. This is because ZAP promoted ADP-ribosylation of core RNAi machinery components [107].

PARP14

PARP14 plays a crucial role in many immune responses, such as macrophage activation [108] and accumulation of type I IFN-inducible proteins [109]. PARP14 contains multiple macrodomains, which can bind to ADP-ribose. Residues in the ADP-ribose binding pocket have been identified to be essential for macrodomain activity [110]. Several viruses, including those from *Coronaviridae*, *Togaviridae*, and *Hepeviridae*, also encode a macrodomain that binds to and counters cellular ADP-ribosylation to combat the immune response [111–113]. SARS-CoV and human CoV 229E with macrodomain-mutant showed increased sensitivity to type I IFN treatment, implying that the CoV macrodomain counters antiviral activities of ISGs [114]. One study demonstrated that PARP14 shows antiviral function in primary macrophage cells during MHV infection, and in human A549 cells with poly(I:C) treatment (Figure 6B) [62]. Specifically, knockdown of PARP12 or PARP14 leads to increased replication of MHV with a mutant-macrodomain (N1347A) but has little impact on wild-type virus in bone marrow-derived macrophages (BMDMs). By using a PARP14-specific inhibitor 8K, along with PARP14^{-/-} BMDMs, A549 and normal human dermal fibroblast cells, the authors further confirm that PARP14 is necessary to enhance the type I IFN induction following coronavirus infection or poly(I:C) stimulation [62]. Consistent with this finding, another study discovered sequence similarity between the ADP-ribose-binding domain of SARS-CoV-2 and PARP14. This suggests coronaviruses coevolve with ADP-ribosylation enzymes to counter the ADP-ribosylation activity of PARPs and their antiviral immune response [115].

The roles of other NAD⁺-consuming enzymes in viral infection

The role of sirtuins

There are seven sirtuins, SIRT1–7, in humans. They regulate diverse functions, including transcription, genome stability, metabolism, and cell signaling via deacetylating various substrate proteins [116,117]. Although the roles of sirtuins in viral infection have not been investigated extensively and the literature does not provide a unifying picture, some evidence points to a protective role of sirtuins in fighting infection. One report showed that all seven sirtuins have broad-range antiviral properties and knocking down any of them promotes the production of virus progeny in infected human cells for many different viruses [118]. The mechanisms behind this promotion are unknown. Protective roles of specific sirtuins in combating infection have been reported as well. SIRT1 promotes the differentiation of Th17 cells [119], which is critical for immune response against microbial infections. Disruption of SIRT1 also increases HPV16 E1–E2 replication [120] and enterovirus 71 replication [121]. SIRT6 promotes TNF α secretion [6,122], dendritic cell differentiation [123], and SIRT6 knockdown is reported to promote viral growth of cytomegalovirus in both fibroblasts and macrophages [124].

In support of a protective role, several well-known properties of sirtuins could provide beneficial effects to fight infections. One of the most established functions of SIRT1 is to promote autophagy and lysosomal function [125,126]. Autophagy and lysosomes are critical for fighting various infections [127]. One well-known function of SIRT3 and SIRT5 is to increase cellular NADPH production by regulating various metabolic enzymes that produce NADPH, such as IDH2 [128,129]. NADPH is required to generate ROS through NADPH oxidases [130]. ROS is a major chemical defense mechanism of our immune system towards microbial infection [130]. Thus, during a severe infection, ROS production increases significantly and SIRT3 and SIRT5 could promote ROS by increasing NADPH production. ROS will also damage normal tissues and thus must be well controlled. Paradoxically, NADPH is also required to repair the oxidative damage caused by ROS to cellular proteins. Thus, sirtuins could also be important for controlling the tissue damage caused by infection.

The role of CD38 and SARM1

The NAD⁺ glycohydrolase CD38 is also important for controlling infections. It is a type I membrane protein with the active site on the extracellular surface of cells (or the luminal side of intracellular organelles). Infection by several viruses, including HIV-1, and by bacteria, is known to trigger CD38 expression [131–133]. In fact, in many cases, CD38 has been used as a marker for immune cell activation [134]. CD38 knockout mice have been shown to have defects in fighting bacterial infection [135–137]. Similarly, the sister protein of CD38, CD157, which is also an ecto NAD⁺ glycohydrolase, has been shown to be important for immune responses [138].

The intracellular NAD⁺ glycohydrolase, SARM1 [29], is a negative regulator of TLR-mediated NF- κ B activation [139,140]. The well-known role of SARM1 in promoting axon degeneration has recently been linked to innate antiviral immune response [141–143]. During la crosse virus (LACV) infection, SARM1 is up-regulated and translocates to the mitochondria where it interacts with MAVS. This eventually leads to neuronal cell death via mitochondrial damage and oxidative stress. Additionally, SARM1 regulates cell survival and cytokine release following inflammasome activation [144]. It is interesting that the same enzymatic activity can either promote or suppress immune responses, depending on the context. SARM1 activation in immune cells, such as cytotoxic T cells, will promote T cell death [30], which could either promote viral infection or serve to prevent over-inflammation after the infection is taken care of. SARM1 activation in virus-infected cells will lead to killing of the infected cells, which may help to limit the spread of the virus [31,32]. Thus, the same biochemical function of SARM1 could lead to different immune outcomes depending on the context, an important point to keep in mind when considering the often conflicting roles of NAD⁺-consuming enzymes in viral infection.

The regulation of NAD⁺ biosynthesis during infections

If NAD⁺-consuming enzymes, especially PARPs, are important in fighting infections, it would be expected that NAD⁺ biosynthesis would also be regulated during infections. This is indeed the case.

In mammals, there are two NAD⁺ biosynthesis pathways, the salvage pathway and the de novo pathway (Figure 1, left) [145]. In the salvage pathway, nicotinate is converted to nicotinate mononucleotide (NaMN) by nicotinate phosphoribosyltransferase (NAPRT), which is then adenylated to generate nicotinate adenine dinucleotide (NaAD⁺) by NaMN adenyltransferase (NMNAT). NaAD⁺ is then converted to NAD⁺ via NAD synthetase. Nicotinamide can be similarly converted to NAD⁺. Nicotinamide riboside, which is present in milk, can also be phosphorylated by its kinases to produce NMN and feed into the salvage pathway [146].

The de novo pathway starts from the amino acid tryptophan. Three heme-dependent enzymes (IDO1, IDO2, and TDO2) can oxidize tryptophan to N-formylkynurenine, which is further processed by four other enzymes to produce nicotinate mononucleotide (NaMN) and feed into the salvage pathway (Figure 1).

Given the above generalization that NAD⁺-consuming enzymes are important for fighting infection, under a severe infection, NAD⁺ will be substantially consumed by these enzymes and thus cells must increase the production of NAD⁺. Indeed, key enzymes in both the salvage and de novo pathways are known to be up-regulated by infections. NAMPT, the rate-limiting enzyme in the salvage pathway, is up-regulated by several different viruses, including HIV and Zika virus [147,148]. Searching publicly available microarray and next-generation sequencing data revealed that NAMPT transcription is significantly up-regulated during many immune-related processes, such as myeloid differentiation [149], lipopolysaccharide (LPS) treatment [150,151], and T cell activation [152]. This transcriptional data is consistent with the idea that under infections, NAD⁺ biosynthesis needs to be increased. One report suggests that NAMPT transcription is controlled by STAT1, which is activated by type I interferons [124]. A recent report showed that NAMPT is up-regulated by SARS-CoV-2 infection in A549 cells, which is also consistent with these earlier findings. However, two other enzymes, NADSYN and QPRT, were down-regulated, suggesting that the regulation of NAD⁺ biosynthesis enzymes is more complicated than we currently understand.

The gatekeepers of the de novo pathway, IDO1/IDO2/TDO2, are also heavily up-regulated during immune activation. IDO1 level and reaction product are up-regulated by human/simian immunodeficiency virus infection [153]. IDO1 induction is through interferon-STAT and is a well-known interferon-induced gene [154]. DNA microarray or next-generation sequencing data also showed that IDO2 and TDO2 are up-regulated by infection or immune activation [151,155–159]. IDO1 is reported to help restrict viral infection [160]. IDO1/IDO2/TDO2 have been well documented to have strong immune modulatory functions [161]. It has been proposed that the intimate connection between IDO1 and immune response is due to the immune modulatory roles of the intermediary metabolites in the de novo NAD⁺ pathway [161] or due to the depletion of

tryptophan [162], which restricts T cell proliferation. However, given that NAD⁺-consuming enzymes could help fight infection, an alternative explanation for the up-regulation of IDO1/IDO2/TDO2 is to promote NAD⁺ biosynthesis. Consistent with this view, the enzyme in the last step of the de novo pathway, quinolinate phosphoribosyltransferase (QPRT), is reported to be an antiviral host factor against Hepatitis C infection [163]. However, QPRT is down-regulated by SARS-CoV-2 infection in A549 cells [28]. Thus, the exact role of this NAD⁺ biosynthesis pathway in fighting viral infection needs to be further investigated. It is possible that viruses have learned to suppress NAD⁺ biosynthesis to evade the host immune response.

The roles of NAD⁺-consuming enzymes like PARPs and dependence on NAD⁺ could also potentially explain the function of NAD⁺ glycohydrolases, CD38 and CD157. These two ecto-enzymes, with their active sites in the extracellular space, serve to mainly degrade extracellular NAD⁺, which is likely released from infected cells sacrificed by cytotoxic T cells and natural killer cells. The degradation products, nicotinamide and ADP-ribose (which can be further degraded to AMP and ribose-5'-phosphate), can be taken up by nearby live immune cells and used to synthesize more NAD⁺. This will in turn help to boost NAD⁺ synthesis and fight the infection. This hypothesis should be tested in future research.

Viruses counteract NAD-mediated host defense

The above discussion on PARPs and sirtuins, regulation of NAD⁺ biosynthesis, and NAD⁺ degrading enzymes provides a unifying hypothesis/model that connects each of them to fighting infections. This model is further supported by findings on the viruses. The genome of SARS-CoV-2 encodes a protein, NSP3, which contains a macrodomain. Macrodomains are evolutionarily conserved and are present in many different virus families, including the *Coronaviridae*, *Togaviridae*, *Matonaviridae*, and *Hepeviridae* families [110]. Macrodomains are known to have two functions. They specifically bind to ADP-ribosylated proteins and thus mediate many of the biological effects of protein ADP-ribosylation [164–166]. In fact, many of the human PARPs proteins that are important for fighting infections contain macrodomains [18]. Therefore, after they modify themselves and substrate proteins, they can also bind to the modified proteins via the macrodomains, which somehow help to achieve their immune-modulatory function. Some macrodomains also have enzymatic activities. They can hydrolyze ADP-ribosyl groups off the modified proteins or small molecules [167–170]. Eight recent reports showed that the macrodomains from different viruses (including coronaviruses) can hydrolyze ADP-ribosyl groups installed by host PARP proteins, thus counteracting the antiviral activities of PARPs. Additionally, the catalytic activity of the viral macrodomain is important for virulence [62,111,112,171–176]. The presence of viral macrodomains to reverse the host PARPs-mediated ADP-ribosylation and the importance of the viral macrodomains for virulence is a strong testament to the importance of PARPs and NAD⁺ in immune responses (Figure 6).

Implications for treating viral infections

The above analysis suggests that host cells deploy NAD⁺-consuming enzymes to fight infection and concurrently boost NAD⁺ biosynthesis to ensure the NAD⁺ supply. However, viruses, including SARS-CoV-2, sabotage this defense mechanism by reversing the effect of PARPs with macrodomains (Figure 7). As alluded to for PARP14, one may suggest the development of small molecule inhibitors for the macrodomains as

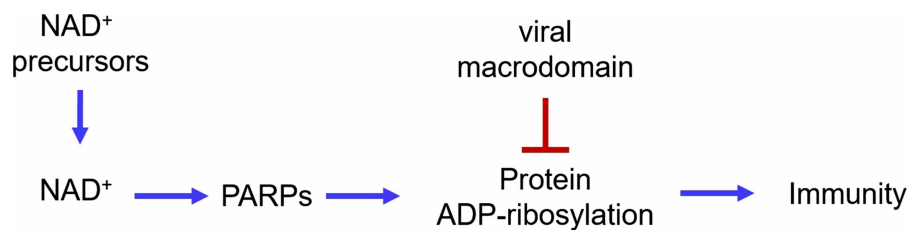


Figure 7. Scheme showing that NAD⁺ and PARPs promote immune responses to fight infections while viral macrodomains inhibit this immune defense mechanism.

Promoting NAD⁺ and PARPs-mediated defense mechanisms, as well as inhibiting viral macrodomains, could potentially help fight viral infections.

antiviral agents. Such inhibitors must be selective for viral macrodomains because if they also bind to host macrodomains, they may interfere with the host's defense mechanism.

Using NAD⁺ biosynthesis precursors (nicotinate, nicotinamide, NR, NMN, and tryptophan) to boost host NAD⁺ biosynthesis could be another potential way to help treat viral infections. This will help to ensure NAD⁺ supply and thus fortify our natural defense mechanism (Figure 7). Given the tug-of-war between the virus and the host, supplying NAD⁺ biosynthesis precursors might help to tip the balance toward clearing the infection. Nicotinate or nicotinamide are already in commonly used vitamin supplements and thus are easily available. In recent years, many researchers and companies are pushing the idea of using NR or NMN to increase NAD⁺ and obtain health benefits [177–182]. These molecules are commercially available due to these efforts. It is still too early to conclude whether NR or NMN would bring health benefits under normal conditions [181–184]. However, given the above analysis, it would be interesting to test whether these NAD⁺ precursors would be beneficial under viral infections.

A counter argument for any beneficial effects of NAD⁺ precursors is that our immune system is already optimized to produce the NAD⁺ needed, and thus supplying extra NAD⁺ precursors may not have much effect. Alternatively, successful pathogens may already have developed strategies to evade the effects of host's NAD⁺-consuming enzymes, and thus increasing the NAD⁺ supply may not be very useful. A recent study showed that this might be the case. Supplying NAD⁺ precursors only helped to fight infections of MHV with an inactive macrodomain, but not wild-type MHV [185].

Another potential antiviral strategy is to use small molecules that can induce the expression of PARPs and thus enhance the antiviral immune response. This is possible as the expression of many PARPs is inducible. While interferons can obviously achieve this, we believe using small molecules to induce PARPs are more ideal. One of the most interesting examples is PARP7. It can be induced by small molecules like TCDD and estradiol, via AHR and ER nuclear receptors [15]. More and safer small molecules that can induce the expression of multiple beneficial PARPs would be highly desirable.

Finally, it is highly possible that any single strategy outlined above will not be good enough to fight viral infections, but a combination of all three will be effective. Thus, as progress is made on the three strategies, testing the combination of them would be very interesting. Furthermore, as we learn more about how viruses counteract the immune response mediated by NAD⁺-consuming enzymes, other therapeutic strategies may also emerge.

Competing Interests

H.L. is a founder and consultant of Sedec Therapeutics.

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Abbreviations

AAV, adeno-associated virus; AHR, aryl hydrocarbon receptor; AIV, avian influenza virus; ARTs, ADP-ribosyltransferases; BMDMs, bone-marrow derived macrophages; DTX3L, Deltex E3 ubiquitin ligase 3L; EBV, Epstein–Barr virus; EMCV, encephalomyocarditis virus; ERK, extracellular signal-regulated kinase; EXOSC5, exosome complex component 5; HA, hemagglutinin; HBV, hepatitis B virus; HSV, Herpes simplex virus; IAV, influenza A virus; ICP0, infected cell protein 0; IFNAR, interferon alpha/beta receptor; ISGs, interferon-stimulated genes; KSHV, Kaposi sarcoma-associated herpesvirus; LANA, latency-associated nuclear antigen; LPS, lipopolysaccharide; MAVS, mitochondrial antiviral-signaling; MHV, mouse hepatitis virus; MLV, murine leukemia virus; NaMN, nicotinate mononucleotide; PARPs, poly-ADP-ribose polymerases; PF, processivity factor; QPRT, quinolinate phosphoribosyltransferase; ROS, reactive oxygen species; RVFV, rift valley fever virus; SARM1, sterile alpha and TIR motif containing 1; TBK, tank binding kinase; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; ZAP, zinc finger antiviral protein.

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