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Interplay between the virus and the ubiquitin–proteasome system: molecular mechanism of viral pathogenesis

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The ubiquitin–proteasome system (UPS) plays a central role in a wide range of fundamental cellular functions by ensuring protein quality control and through maintaining a critical level of important regulatory proteins. Viruses subvert or manipulate this cellular machinery to favor viral propagation and to evade host immune response. The UPS serves as a double-edged sword in viral pathogenesis: on the one hand, the UPS is utilized by many viruses to maintain proper function and level of viral proteins; while on the other hand, the UPS constitutes a host defense mechanism to eliminate viral components. To combat this host anti-viral machinery, viruses have evolved to employ the UPS to degrade or inactivate cellular proteins that limit viral growth. This review will highlight our current knowledge pertaining to the different roles for the UPS in viral pathogenesis.

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Introduction

Viruses have evolved to exploit the host cellular machinery to establish productive infection. In eukaryotic cells, the ubiquitin–proteasome system (UPS) is the major intracellular pathway for degradation and functional modification of cellular proteins. It plays a key role in the regulation of many fundamental cellular processes, including apoptosis, cell cycle regulation, signal transduction, antigen processing, and transcriptional regulation [1]. Ubiquitin is a small (76 amino acids) and highly conserved protein present in almost all eukaryotic cells. For UPS-mediated proteolysis, protein substrates are first labeled with ubiquitins (a process called ubiquitination),

and then recognized and degraded by the 26S proteasome [1]. Ubiquitination occurs via a sequential reaction mediated by three enzymes, i.e. the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2), and the ubiquitin ligase (E3). The substrate specificity to the ubiquitin conjugation system is determined by the E3 ligases [2]. After multiple rounds of ubiquitination, a poly-ubiquitin chain is formed and serves as a signal for substrate recognition and degradation by the 26S proteasome. Ubiquitin is then released through the activities of deubiquitinating enzymes (DUBs) [1,2]. In addition to ubiquitin-dependent degradation, some cellular proteins can also be destroyed by the proteasome in a ubiquitin-independent manner. This process requires the function of proteasome activator 28 (PA28, also known as REG) [3].

Besides the role of poly-ubiquitination (most commonly linked with lysine 48) in proteasomal degradation, ubiquitination is also involved in regulating protein function without targeting for degradation. Mono-ubiquitination or lysine 63-linked poly-ubiquitination has been shown to play key roles in a wide range of cellular functions, including protein subcellular localization, transcription, DNA repair, and signal transduction [2,4]. Apart from ubiquitination, target proteins can also be post-translationally modified by several ubiquitin-like proteins, such as the small ubiquitin-like modifiers (SUMO, four isoforms are identified in humans, SUMO1, SUMO2, SUMO3, and SUMO4) [5,6] and the interferon-stimulated gene 15 (ISG15) [7,8]. Protein modification mediated by SUMO and ISG15 (termed sumoylation and ISGylation, respectively) occurs in a manner similar to ubiquitination that requires an enzymatic cascade of E1 (Aos1/Uba2 heterodimer for SUMO and UBE1L for ISG15), E2 (Ubc9 for SUMO; UbcH8 and UbcH6 for ISG15), and E3 [5–8]. There are currently three identified SUMO E3s, that is, RanBP2, PIAS and the Polycomb protein Pc2 [5,6] and three known ISG15 E3s, that is, HERC5, HHARI, and TRIM25 [7,8]. These processes can be reversed via the action of de-sumoylating or de-ISGylating enzymes. The sumoylation and ISGylation conjugation systems have been implicated in the regulation of many cellular functions, including transcriptional regulation, anti-viral immune response, signaling pathways, and vesicular trafficking [5–8].

Accumulating evidence has pointed to important roles for the host UPS in the regulation of viral pathogenesis. It has

become increasingly evident that viruses interact with the UPS at multiple levels. They can either directly encode proteins with E3-like or DUB-like activities or modify specific aspects of the host UPS function for their own advantages [9–11]. The UPS plays a dual role in viral pathogenesis: it has both pro-viral and anti-viral effects [9–11]. The UPS can enhance the function of viral proteins via post-translational modification mediated by ubiquitin or ubiquitin-like proteins. It can also facilitate viral infection through controlling the stability of both viral and cellular proteins. However, on the other hand, UPS-mediated viral protein degradation may also constitute a host defense process against viral infections. Viruses have developed sophisticated mechanisms to counteract this anti-viral immune response. This review will focus on how viruses evolve to interact with the host UPS to favor their propagation, to escape host immune response, and contribute to viral pathogenesis.

Viral degradation of cellular proteins by the UPS

Some cellular proteins can function as restriction factors to limit viral infection by directly inhibiting viral replication or through controlling the state of their infected cells, in particular cell survival/apoptosis and cell cycle progression. For example, the tumor suppressor protein p53 has been shown to block viral replication by suppressing viral gene activation and/or through promoting host cell apoptosis [12,13]. Viruses can recruit the cellular E3 ligases to target anti-viral proteins for degradation. Several proteins encoded by DNA tumor viruses, such as the human papillomavirus (HPV) E6 and E7 proteins [14,15] and the adenovirus E1B55k/E4orf6 proteins [16], have been shown to induce the assembly of an E3 ligase complex that contains both viral protein and cellular E3 to catalyze the ubiquitination of p53 and subsequent degradation by the proteasome. For instance, the HPV E6 protein binds to the cellular E3 ligase E6-associated protein (E6AP) to form an E3 complex to mediate p53 degradation [14]. In addition to p53, the HPV E7 protein also targets another tumor suppressor protein, retinoblastoma protein (pRb), for proteasomal degradation, which is mediated through a cullin E3 complex [17]. Beside ubiquitin conjugation, the expression of p53 can also be regulated at the levels of deubiquitinating and proteasome activity. It was shown that the Epstein-Barr nuclear antigen 1 interacts with the ubiquitin-specific protease 7 (USP7, a cellular DUB) to enhance p53 degradation, presumably through inhibiting the activity of USP7 and thereby preventing p53 deubiquitination [18]. In the case of coxsackievirus infection, it was found that proteasome activator PA28 γ is relocated from the nucleus to the cytoplasm where it facilitates the turnover of p53 through the proteasome [19]. Another example of viral manipulation of the UPS for cellular protein degradation is provided by lentivirus destruction of the SAMHD1 (sterile alpha motif domain- and histidine-aspartate domain-containing protein 1) protein.

SAMHD1 is a cellular deoxynucleoside (dNTP) triphosphohydrolase that inhibits human immunodeficiency virus (HIV) infection by suppressing the activity of reverse transcriptase through depleting cellular dNTPs [20]. It has been recently demonstrated that the viral protein X encoded by HIV-2 and some simian immunodeficiency virus redirects a cullin-RING E3 ligase to SAMHD1 to target it for proteasomal degradation in the nucleus [21*].

A common strategy for viral evasion of host immune surveillance is to target host immune adaptor and signaling molecules (e.g. molecules involved in type I interferon (IFN) response and MHC class I antigen presentation) for proteasomal degradation or to prevent the destruction of immune-related transcription factor inhibitors (e.g. I κ B α , an inhibitor of the nuclear factor kappa B (NF κ B) by sequestering it in the cytoplasm). Early studies have revealed that human cytomegalovirus (HCMV)-encoded proteins, US2 and US11, induce the dislocation of MHC class I from the endoplasmic reticulum to the cytosol, where ubiquitination and proteasomal degradation of MHC molecules take place [22,23]. Recent work has identified additional cellular targets (integrin α -chains, CD112, interleukin-12, PTPRJ (protein tyrosine phosphatase, receptor type, J), and thrombomodulin) for US2 protein, which are ubiquitinated and degraded through the recruitment of the cellular E3 ligase (TRC8) [24*]. Together, these studies suggest that US2 acts as a degradation hub modulating multiple host immune responses to HCMV infection. In addition to MHC class I, the Janus kinase-signal transducers and activators of transcription (JAK/STAT) and NF κ B pathways also play critical roles in host anti-viral defense. Viruses have developed distinct mechanisms to utilize the UPS to dampen these host innate immune responses. One such example is the V protein of paramyxoviruses, including mumps virus, simian virus 5, and parainfluenza virus type 2, which promotes UPS-dependent STAT degradation through co-opting a host cellular E3 ligase [25–27]. Similarly, the dengue virus NS5 protein was also found to stimulate proteasomal degradation of STAT2, thus blocking type I IFN signaling [28]. Moreover, it was recently reported that the ORF61 protein encoded by simian varicella virus and varicella zoster virus prevents ubiquitination and degradation of I κ B α , most likely through interacting with β -transducin repeat containing protein, a subunit of the Skp1-Cul1-F-box (SCF) E3 complex, thereby suppressing NF κ B-mediated immune responses [29*]. RNA silencing is an important host defense mechanism against viral infection in plants [30]. To combat this anti-viral immunity, several plant viruses encode proteins to target key components of RNA silencing, such as the ARGONAUTE1 protein [31,32], for proteasomal degradation. Together, hijacking the UPS is a common viral strategy to evade host immune response.

In addition to its pro-viral function usurped by viruses as discussed above, the UPS-mediated cellular protein degradation may also represent a host defense mechanism against viral infection. For example, the Rar1 protein, a critical downstream product of the N gene of tobacco, was shown to interact with SGT1, a highly conserved component of SCF E3 complex, and COP9 signalosome, a multi-protein complex involved in UPS-mediated protein degradation [33]. Inhibition of SGT1 and COP9 abolishes the N gene-mediated resistance to Tobacco mosaic virus, suggesting a key role for the UPS in the regulation of plant innate immune response [33,34]. Further study revealed that this anti-viral effect can be counteracted by geminivirus-encoded C2 protein, which inhibits SCF activity and interferes with the function of COP9 signalosome [35].

Viral protein degradation by the UPS

The UPS serves as either a pro-viral or anti-viral mechanism in the context of controlling the levels of viral proteins. Proper ratio of structural over non-structural viral proteins is critical for productive viral infection [36,37]. Viruses have employed the UPS to keep some viral proteins, mostly non-structural proteins, such as RdRp that has been demonstrated to interfere with viral packaging and even become anti-viral at high amounts [37,38], at a relatively low level. Multiple studies have shown that the abundance of RdRp encoded by Turnip yellow mosaic virus [39], Sindbis virus [40], hepatitis C virus (HCV) [41], and hepatitis A virus (HAV) [42] is tightly controlled via the UPS. Similarly, previous reports on picornavirus have revealed that the 3C protease of encephalomyocarditis virus and HAV is rapidly degraded via the UPS and present in low concentrations in infected cells [43–45]. Furthermore, HCV-encoded proteases NS2/3, were found to be degraded following viral infection in a phosphorylation-dependent manner mediated by casein kinase 2 [46]. Another example of viral non-structural protein degradation is provided by the HPV E7, which is ubiquitinated and degraded through two independent pathways [47,48]. One involves the IFN- γ -inducible suppressor of cytokine signaling-1 (SOCS1), a member of the STAT signaling pathway, and takes place in the cytoplasm [47]. The other requires the SCF E3 complex, which induces E7 ubiquitination with the assistance of E2 enzyme UbcH7 and subsequent degradation in the nucleus [48].

In addition to being a viral strategy for its effective infection, it is also conceivable that maintaining a low level of viral proteins represents a viral mechanism to evade recognition by the host immune system. Alternatively, degradation of viral proteins constitutes a host defense mechanism. In the latter case, some viral structural proteins are demonstrated to be the targets of the UPS. For example, West Nile virus capsid protein is ubiquitinated by the cellular E3 ligase, Makorin ring finger protein 1, followed by proteasomal degradation [49]. It was also shown that the core protein of HCV is

degraded via proteasome in both ubiquitin-dependent through recruiting E3 ligase E6AP and -independent manner mediated by proteasome activator PA28 γ [50]. The movement proteins of several plant viruses are also degraded through the UPS [51,52]. Moreover, it was found that the host protein Rsp5p, a member of the Nedd4 (neuronal precursor cell-expressed developmentally downregulated 4) family of E3 ligases, binds to the p92 replication protein of Tomato bushy stunt virus and promotes its degradation and consequent inhibition of viral replication [53]. Thus, degradation of some viral proteins can also be a host anti-viral defense mechanism.

Viral protein modification by ubiquitin and ubiquitin-like modifier

Post-translational modification of protein with ubiquitin and ubiquitin-like proteins constitutes an important mechanism to regulate viral protein function. Studies from different groups have shown that ubiquitination of the Gag protein of retroviruses is required for its function in viral budding and release [54–56]. The late budding domain in the Gag protein carries conserved motifs, such as PPXY and PTAP, that recruit host WW domain-containing HECT E3 ligase, Nedd4 to catalyze the ubiquitination of Gag [57,58]. Other than Nedd4, the tumor susceptibility gene 101 (Tsg101), also binds to the consensus motif in Gag and such interaction is required for viral budding and release [59,60]. Tsg101 is a protein of the endosomal sorting complex required for transport (ESCRT) complex and is involved in vacuolar protein sorting and biogenesis of multivesicular body. Similarly, it was found that the p33 replication protein of Tomato bushy stunt virus is ubiquitinated and this modification does not affect its stability, but instead enhances its interaction with ESCRT proteins, contributing to effective viral replication [61,62]. Moreover, ubiquitination of the HIV-1 Tat protein and the human T-cell leukemia virus type 1 Tax protein was demonstrated to enhance their transactivation activities without targeting them for degradation [63,64]. The RNA-dependent RNA polymerase (RdRp) encoded by coxsackievirus provides another example of viral protein ubiquitination and activation during infection [65]. Finally, certain viral structural proteins, such as the envelope protein of severe acute respiratory syndrome coronavirus (SARS-CoV) [66] and structural proteins of several plant viruses [67], were also found to be ubiquitinated although the functional consequence of such modification remains elusive.

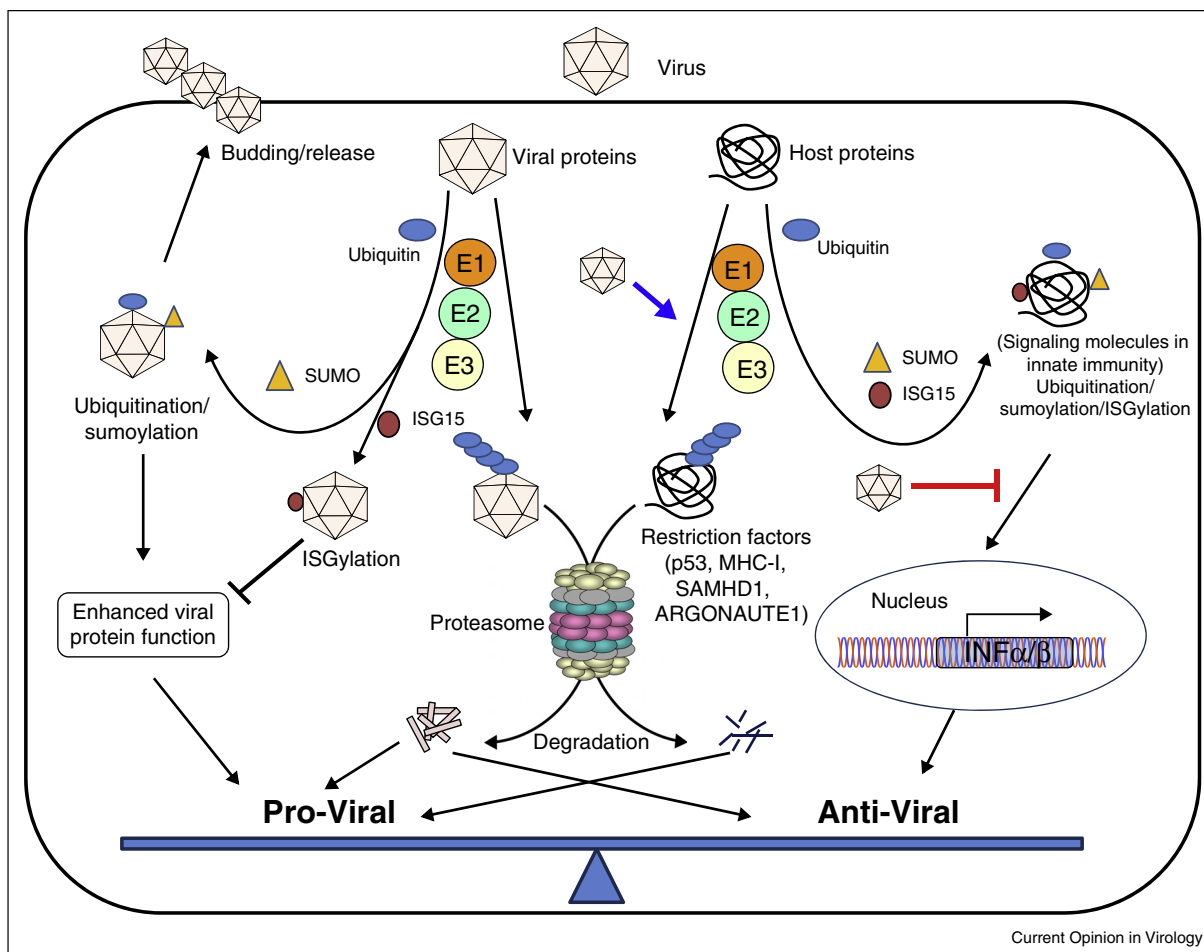
Some viral functions also require SUMO modification. For example, the immediate-early (IE) IE1 and IE2 proteins of HCMV are covalently modified by SUMO following infection [68,69]. Although the exact role of sumoylation in viral pathogenesis is still unclear, sumoylation-resistant mutant of HCMV IE1 was found to exhibit attenuated viral growth, indicating a role for SUMO modification in regulating viral protein function and

replication [70]. The adenoviral E1B55k protein is another example of viral protein modification by SUMO and this modification appears to be required for its function in modulating cell cycle progression and apoptosis as a sumoylation-deficient mutant of E1B55k fails to interact with p53 and inhibit p53-mediated transactivation [71,72]. Furthermore, it was reported that the papillomavirus E1 protein interacts with SUMO E2 enzyme Ubc9 and E3 enzyme PIAS to support viral replication and disruption of their association leads to reduced viral virulence [73,74]. Besides animal viruses, viral protein modification by SUMO was also observed in plant viruses. It was found that

the RepAC1/Rep protein, encoded by Tomato golden mosaic virus and Tomato yellow leaf curl Sardinia virus, binds to SCE1 (SUMO-conjugating enzyme), a plant homology to Ubc9, and sumoylation plays an important role in viral replication [75]. It was also demonstrated that the RdRp of Turnip mosaic virus undergoes SUMO modification via its interaction with SCE1 and such modification is required for viral infection [76].

ISG15 and the ISGylation conjugation system represent an important host defense mechanism against infection of a broad spectrum of viruses, including Sindbis virus,

Figure 1



Viral interaction with the host ubiquitin–proteasome system (UPS): pro-viral and anti-viral function of the UPS in viral pathogenesis. The UPS, including modification of key signaling molecules involved in innate immunity by ubiquitin or ubiquitin-like modifiers (e.g. SUMO and ISG15), represents an important host anti-viral defense mechanism. Many viruses have evolved to subvert or manipulate this cellular machinery to favor their growth and to escape host immune response. In some cases, viruses encode proteins with E3 activity or even becoming part of cellular E3 complex to degrade cellular proteins (e.g. p53, MHC-I, SAMHD1, ARGONAUTE1) that limit viral growth (blue arrow). In others they generate proteins with de-ubiquitinating or de-ubiquitinating-like activity to interfere with the host ubiquitin or ubiquitin-like (e.g. SUMO and ISG15) conjugation system to combat the host anti-viral signaling pathways (red lines). Viral protein modification by ubiquitin or SUMO is often associated with increased viral release and replication, whereas modification by ISG15 results in reduced viral protein function. Viral protein degradation is either a reflection of viral clearance by host immune response or a viral strategy to maintain an optimal level of viral protein to ensure efficient viral production. *Abbreviations:* E1, ubiquitin/SUMO/ISG15-activating enzyme; E2, ubiquitin/SUMO/ISG15-conjugating enzyme; E3, ubiquitin/SUMO/ISG15 ligase; ISG15, interferon-stimulated gene 15; MHC-I, major histocompatibility; SAMHD1, sterile alpha motif domain-containing protein 1 and histidine-aspartate domain-containing protein 1; $INF\alpha/\beta$, interferon- α/β .

Table 1**Interplay between the viruses and the ubiquitin-proteasome system**

Function (confirmed or proposed)	Virus	Viral proteins that manipulate the UPS function	Target proteins (host or viral proteins)	Actions of the UPS	References	
Pro-viral function through regulating cellular protein degradation	HPV	E6, E7	p53, pRb	Degradation (except for I κ B α whose stability is enhanced)	[14,15,17]	
	Adenovirus	E1B55k, E4orf6	p53		[16]	
	EBV	EBNA1	p53		[18]	
	Coxsackievirus	Vpx	p53		[19]	
	HIV-1, HIV-2	US2, US11	SAMHD1		[20,21*]	
	HCMV	V	MHC-1, Integrin α -chain, CD112, IL-12, PTPRJ, thrombomodulin		[22,23,24*]	
	Mumps virus, SV5, PIV5	NS5	STAT1, STAT2		[25-27]	
	Dengue virus	ORF6	STAT2		[28]	
	SVV, VZV	P25	I κ B α		[29*]	
	PVX	P0	ARGONAUTE1		[31]	
Enamovirus		ARGONAUTE1	[32]			
Pro-viral function via maintaining proper levels of viral proteins	TYMV, SINV, HCV, HAV		RdRp	Degradation	[39-42]	
	EMCV, HAV		3 C		[43-45]	
	HCV		NS2/3		[46]	
	HPV		E7		[47,48]	
Pro-viral function through enhancing viral protein activities by ubiquitination or sumoylation	Retroviruses		Gag	Ubiquitination	[54-56]	
	TYMV		p33		[61,62]	
	HIV-1		Tat		[63]	
	HTLV-1		Tax		[64]	
	Coxsackievirus		RdRp		[65]	
	SARS-CoV		Envelope protein		[66]	
	BSMV, BMV, CPMV, SPMV, CPMV,		Structural protein		[67]	
	HCMV		IE1, IE2		Sumoylation	[68-70]
	Adenovirus		E1B55k		[71,72]	
	Papillomavirus		E1		[73,74]	
TGMV & TYLCSV		RepAC1/Rep	[75]			
TMV		RdRp	[76*]			
Anti-viral function through degradation of viral proteins	WNV		Capsid protein	Degradation	[49]	
	HCV		Core protein		[50]	
	TYMV, TMV		Movement protein		[51,52]	
	TBSV		p92		[53]	
Anti-viral function via suppressing viral protein activity by ISGylation	Influenza A virus		NS1	ISGylation	[83]	
	HPV		L1		[84]	
	Coxsackievirus		2A		[85**]	

Table 1 (Continued)

Function (confirmed or proposed)	Virus	Viral proteins that manipulate the UPS function	Target proteins (host or viral proteins)	Actions of the UPS	References
Pro-viral function by counteracting the post-translational modification of signaling molecules involved in innate immunity	HSV-1	UL36	TRAF3	De-ubiquitination	[89*]
	KSHV	ORF64	RIG-I		[90]
	SARS-CoV	PLpro	Signaling molecules involved in innate immunity		[96*]
	Nairoviruses, Arteriviruses	Ovarian tumor domain protease			[97,98]
	Influenza B virus	NS1	Signaling molecules involved in innate immunity	De-ISGylation	[94]
	Vaccinia virus	E3			[95]
SARS-CoV	PLpro			[96*]	
Nairoviruses, Arteriviruses	Ovarian tumor domain protease			[97]	

Abbreviations: HPV, human papillomavirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HCMV, human cytomegalovirus; SV5, simian virus 5; PIV5, parainfluenza virus 5; SVV, simian varicella virus; VZV, varicella zoster virus; PVX, potato virus X; TYMV, turnip yellow mosaic virus; SINV, Sindbis virus; HCV, hepatitis C virus; HAV, hepatitis A virus; EMCV, encephalomyocarditis virus; HTLV-1, human T-cell lymphotropic virus-1; SARS-CoV, severe acute respiratory syndrome coronavirus; BSMV, barley stripe mosaic virus; BMV, brome mosaic virus; CPMV, cowpea mosaic virus; SPMV, satellite panicum mosaic virus; CPSMV, cowpea severe mosaic virus; TGMV, tomato golden mosaic virus; TYLCSV, tomato yellow leaf curl Sardinia virus; TMV, Tobacco mosaic virus; WNV, West Nile virus; TBSV, Tomato bushy stunt virus; HSV-1, herpes simplex virus-1; KSHV, Kaposi's sarcoma-associated herpesvirus; pRb, retinoblastoma protein; EBNA1, Epstein-Barr nuclear antigen 1; Vpx, viral protein x; SAMHD1, sterile alpha motif domain- and histidine-aspartate domain-containing protein 1; MHC-1, major histocompatibility-1; IL-12, interleukin-12; PTPRJ, protein tyrosine phosphatase, receptor type, J; STAT, signal transducers and activators of transcription; PLpro, papain-like protease; TRAF3, TNF receptor associated factor 3; RIG-I, retinoic acid inducible gene 1; RdRp, RNA-dependent RNA polymerase.

Ebola virus, influenza virus, coxsackievirus, vaccinia virus, vesicular stomatitis virus, Sendai virus, Newcastle disease virus, HPV, HIV-1, dengue virus, West Nile virus, and Japanese encephalitis virus [77^{••}]. Expression of ISG15 is highly inducible by type I IFN upon viral infection [7]. Animal studies have shown that mice with ISG15^{-/-} or UBE1L^{-/-} (which lack the ISG15 conjugating enzyme) are more susceptible to various viral infections and develop more severe tissue damage [78–80]. The mechanism of the anti-viral property of ISG15 remains largely unclear. Recent studies suggest that it involves the protective function of unconjugated ISG15 against viral infection and post-translational modification of both host and viral proteins [77^{••}]. It has been shown that expression of ISG15 blocks the activity of Nedd4, thereby inhibiting ubiquitination of HIV-1 Gag and Tsg101 proteins and Ebola viral matrix proteins (VP40), which are necessary for viral budding/release [81,82]. Moreover, viral protein ISGylation has been revealed to also contribute to the type I IFN-mediated anti-viral response. Although the precise mechanisms remain to be established, available evidence supports a loss-of-function mechanism of ISG15 modified viral proteins. It was reported that ISGylation of the influenza A virus NS1 protein via the function of the E3 ligase UERC5 results in impaired viral replication [83]. Similarly, modification of the HPV L1 capsid protein by ISG15 is linked to decreased viral production [84]. In coxsackievirus infection, it was found that ISG15 modification of 2A protease attenuates its activity in cleaving host eukaryotic translation initiation factor 4G, thereby counteracting host translation shutoff during viral infection [85^{••}].

Viral modulation of host protein modification by ubiquitin and ubiquitin-like modifier

In addition to their role in regulating viral protein function, modification by ubiquitination and sumoylation has emerged as a central host anti-viral mechanism through modulating the function of key signaling molecules involved in innate immunity, such the pattern recognition receptor signaling pathway and the NFκB pathway (see reviews [86,87^{••},88^{••}] for the details). There is increasing evidence that viruses have evolved strategies to block these processes to evade host innate immune responses. For example, herpes simplex virus 1 encodes the largest tegument protein, UL36, which acts as a DUB to remove ubiquitin chains from TNF receptor associated factor 3 (TRAF3) and consequently inhibits IFN-β signaling [89[•]]. Similarly, the ORF64 protein encoded by Kaposi's sarcoma-associated herpesvirus hydrolyzes ubiquitin chains from retinoic acid inducible gene 1 (RIG-I), resulting in decreased production of IFN [90].

Besides viral proteins, a number of anti-viral host proteins, such as interferon regulatory factor 3 [91], RIG-I [92], and protein kinase R [93], have been shown to undergo ISGylation, resulting in a gain-of-function of these proteins and consequent anti-viral immune response. To overcome host

innate defense, viruses have evolved to interfere with the ISG15 conjugation system to antagonize its anti-viral activity. For instance, it was reported that the influenza B virus NS1 [94] and vaccinia E3 protein [95] interact with ISG15 to prevent it from binding to UBE1L, thus inhibiting the formation of ISG15 conjugates. Furthermore, some viruses can encode their own deISGylating enzyme to disrupt ISG15 conjugation. For example, the papain-like protease of SARS-CoV [96[•]] and the ovarian tumor domain-containing protease of nairoviruses and arteriviruses [97,98] possess both deISGylating and deubiquitinating activity that counteracts the post-translational modification of signaling molecules involved in the innate immune response.

Conclusion

Growing evidence has indicated a dual role for the UPS in viral pathogenesis (summarized in Figure 1 and Table 1). The UPS may represent a host defense mechanism against viral infection, or they may be hijacked by the virus to enhance its infectivity. Viral manipulation of the UPS has emerged as a central immune evasion mechanism. Viruses evolve to inhibit many facets of the host anti-viral immune response. In some cases, viruses produce proteins to mimic the function of the UPS or to redirect the cellular E3 to allow for targeted degradation of cellular factors or viral proteins that might hinder viral replication. In others cases, they encode proteins to interfere with the host ubiquitin or ubiquitin-like (e.g. SUMO and ISG15) conjugation system to inactivate the host anti-viral signaling pathways. In many cases, these mechanisms work together to dynamically modulate the function of the UPS to gain maximal viral infection. A better understanding of the complicated interaction between the virus and the host UPS with further identification of the new targets for viral E3s or DUBs and careful characterization of the functional consequence of the ubiquitin modification or degradation events will provide novel insights into the mechanism of viral pathogenesis, facilitate the discovery of new immune modulators, and promote the development of efficient antiviral interventions.

Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

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