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Review article

Pleiotropic roles of the ubiquitin-proteasome system during viral propagation

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ABSTRACT

Protein ubiquitination is a highly conserved post-translational modification affecting various biological processes including viral propagation. Ubiquitination has multiple effects on viral propagation, including viral genome uncoating, viral replication, and immune evasion. Ubiquitination of viral proteins is triggered by the ubiquitin-proteasome system (UPS). This involves the covalent attachment of the highly conserved 76 amino acid residue ubiquitin protein to target proteins by the consecutive actions of E1, E2 and E3 enzymes, and the 26S proteasome that together form a multiprotein complex that degrades target proteins. The UPS is the primary cytosolic proteolytic machinery for the selective degradation of various forms of proteins including viral proteins, thereby limiting viral growth in host cells. To combat this host anti-viral machinery, viruses have evolved the ability to employ or subvert the UPS to inactivate or degrade cellular proteins to favour viral propagation. This review highlights our current knowledge on the different roles of the UPS during viral propagation.

1. Introduction

Increasingly convincing evidence indicates that various human diseases, including cancer, neurodegenerative, and cardiovascular diseases, are directly related to the excessive accumulation of aggregated or misfolded proteins in cells [1–4]. Therefore, it is important to maintain the homeostatic balance between protein synthesis and degradation in eukaryotic cells. It is generally accepted that eukaryotic organisms have developed the ubiquitin-proteasome system (UPS) and autophagy-lysosome system (ALS) for selective degradation of structurally abnormal proteins in cells [5, 6]. The UPS is responsible for the degradation of most cytosolic short-lived proteins and misfolded proteins, while the ALS degrades long-lived bulk proteins, including cytosolic proteins, organelles, aggregates and extracellular proteins imported into the cell by endocytosis or pinocytosis [7, 8]. During ubiquitination, one (monoubiquitination) or more (polyubiquitination) highly conserved 76 amino acid ubiquitin (Ub) chains are covalently attached to a lysine residue of the target protein via a cascade of enzymatic reactions catalysed by ubiquitination enzyme (E1), ubiquitin-transferring enzyme (E2), and ubiquitin ligase (E3). Firstly, Ub is activated by E1 in an ATP-dependent manner, then is transferred to form a thioester bond with E2; finally, E3 promotes the transfer of Ub from E2 to the Lys of the target protein [9]. A single Ub molecule conjugated to the Lys residue of a substrate is referred to as monoubiquitination, while polyubiquitination involves the attachment of multiple Ub chains. Subsequently, the tagged substrates are deubiquitinated by deubiquitinating enzymes (DUBs), Ub molecules are released from substrates by enzymatic steps, and deubiquitinated substrates are degraded into small peptides by the 26S proteasome. The 26S proteasome is composed of a 20S catalytic core and two 19S regulatory caps on both ends of the 20S core [10, 11]. A simplified schematic diagram showing the steps involved in the degradation of tagged proteins is shown in Fig. 1 A.

The typical virus life cycle sequentially involves cell entry, viral genome uncoating, transcription, replication, protein expression, particle assembly, and egress along with immune evasion. These processes require a large subset of the host cell machinery, including the host UPS. Ub is an evolutionarily highly conserved and ubiquitously expressed polypeptide with seven internal lysine residues (K6, K11, K27, K29, K33, K48 and K63) as shown in Fig. 1B, and only three amino acids differ between yeast and human Ub homologues [12, 13]. Therefore, there are eight possible positions for the second Ub to attach (including the amine group at the N-terminus), and the functional diversity of this modification is expanded by polyubiquitination. The best-characterised K48-linked polyubiquitination is commonly involved in Ub-dependent proteolysis [14]. Other linkage types, such as K63,

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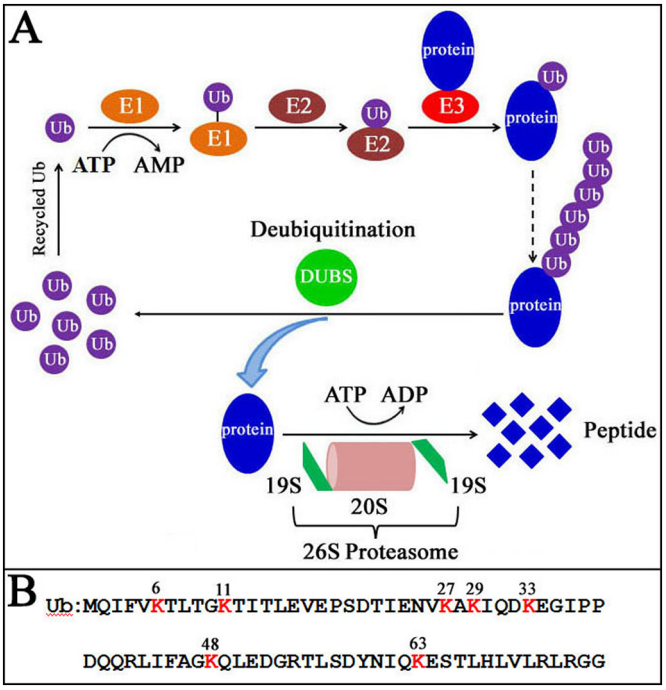

Fig. 1. Degradation of tagged proteins by the ubiquitin-proteasome system (UPS) and the amino acid sequence of ubiquitin (Ub). (A) In this selective proteolytic pathway, Ub is first activated by E1, subsequently transferred to the E2 enzyme, and finally covalently attached to the target substrate. Proteins with polyubiquitin chains are recognised by deubiquitinating enzymes (DUBS) that release Ub, and deubiquitinated proteins are further degraded into small peptides by the 26 proteasome. The 26S proteasome is composed of a 20S catalytic complex and two 19S regulatory complexes. (B) The seven lysine residues in the Ub molecule are coloured red, and their corresponding numbering in the amino acid sequence of Ub is indicated above the red letters. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

serve as signals for the regulation of protein endocytosis, sorting, cellular trafficking, and innate immune signalling [15, 16]. Additionally, some atypical linkages such as Lys6, Lys11, Lys29, and Met1 are reported to participate in proteasomal or lysosomal degradation of proteins and nonproteinaceous cellular constituents [17]. Ubiquitination has always been associated with protein degradation. However, some atypical linkages and new roles for Ub in viral propagation have emerged in recent years [18–20]. In this review, we highlight recent progress in the field that advances our understanding of the molecular regulation of viral propagation by protein ubiquitination.

2. Identification of viral proteins modified by ubiquitination

Ubiquitination involves the covalent conjugation of Ub to lysine residues of target proteins. The best-characterised linkages are Lys48- and Lys63-linked polyubiquitination, of which Lys48 is the most prominent linkage that targets proteins for degradation via the 26S proteasome [21]. By contrast, Lys63-linked polyubiquitin chains perform a signalling function in various cellular processes such as DNA repair, apoptosis and autophagy [22]. Moreover, some atypical Lys linkages (Lys6, Lys11, Lys27, Lys29 and Lys33) have been examined by mass spectrometry and found to mediate various non-proteolytic processes such as trafficking, signalling and autophagy [23, 24].

To date, many viral proteins have been reported to be ubiquitinated, including influenza A virus-encoded NP, M2 and PB1 [25–28], Dengue Virus-encoded NP [29], and 54 viral proteins encoded by the well-characterised cowpox virus strain [30]. In ubiquitinated proteins, Ub is frequently found to be covalently conjugated to Lys residues, but non-Lys residues of substrates such as serine (Ser), threonine (Thr) and cysteine (Cys) are also modified in rare cases. For example, Wang et al. reported that Thr10 and Cys37 of the retroviral integrase are ubiquitinated [31], and Patnaik et al. reported that the C-terminalglycine (Gly) of retrovirus Gag is ubiquitinated to direct viral budding and particle release [32]. In addition to the ubiquitination of viral proteins, Cadwell and Coscoy reported the ubiquitination on non-lysine residues by a viral E3 ubiquitin ligase encoded by Kaposi's sarcoma-associated herpesvirus [33], and mutagenesis revealed that ubiquitination can occur on serine, threonine or lysine residues within the cytoplasmic tail of major histocompatibility complex molecules [34]. Ubiquitination on non-lysine residues may directly interfere with the three-dimensional structure of target proteins, thereby changing their functions. Thus, identification of non-lysine ubiquitination sites is also important for understanding the mechanisms that underlie the ubiquitin-mediated degradation of viral proteins.

3. Viruses manipulate the UPS to favour viral propagation

The UPS plays an important role in the regulation of cellular environmental homeostasis during viral infection. The UPS is a double-edged sword in viral pathogenesis; host cells employ the UPS to degrade viral proteins to limit viral infection, but viruses can manipulate the UPS machinery to degrade cellular restriction factors, thereby facilitating viral propagation. To date, many viruses have been reported to reprogram the UPS to satisfy their needs, and the UPS can function in different stages of the viral life cycle, including viral capsid uncoating [35, 36], viral replication [37–39], gene transcription [40, 41], viral envelopment [42], and viral progeny release [43, 44]. Furthermore, the UPS was reported to play an important role during various stages of the coronavirus (CoV) infection cycle [45], and it could potentially be developed as a drug target to modulate the impact of CoV infection in the future.

The UPS can be manipulated by many viruses to facilitate viral replication, but the proteasome inhibitor MG132 can inhibit viral replication [20, 46, 47]. For example, the replication of some viruses such as human astrovirus [47], vaccinia virus [48], tombusvirus [49], hepatitis E virus [50, 51], porcine circovirus type 2 [52], and Ebola virus [53] are regulated by the UPS, and recent studies revealed that the UPS is necessary for the efficient replication of African swine fever virus and human astrovirus [20, 47]. Among these viruses, some encode specific proteins that modify the host Ub machinery. For example, human immunodeficiency virus auxiliary protein, Vif, Vpx, and Vpu can hijack the UPS to facilitate viral propagation in host cells [54]. Some viruses even encode their own ubiquitinating or deubiquitinating enzymes (DUB), and a total of 28 viruse-encoded DUBs including herpesviral DUBs were summarized by Bailey-Elkin et al. [55]. Some DUBs can help to evade host antiviral innate immunity to enhance viral replication. For example, BPLF1 of three DUBs encoded by EBV genome was reported to contributes to innate immune evasion through interference with toll-like receptor signalling [56], and arterivirus papain-like protease 2 with the activity of DUB can suppresses the innate immune response in infected host cells [57]. Moreover, NP, M2 and PB1 proteins of influenza A virus are ubiquitinated, and this affects replication of the viral genome [25–28]. Furthermore, Kirui et al. revealed that ubiquitination can up-regulate influenza virus polymerase activity, directly enhancing viral RNA synthesis [58]. In summary, various effective strategies have been developed by viruses during natural evolution to facilitate viral propagation.

The decomposition of the viral capsid is necessary for viruses to release the viral genome prior to its replication in host cells. Some viral capsids were reported to be ubiquitinated and further degraded by the UPS, which facilitates the transfer of the viral genome into the cytosol during viral propagation. For example, Byk et al. reported that the Dengue virus capsid protein was degraded by a UPS-dependent process, which may be involved with the initial rounds of viral translation and

Table 1
The different roles of UPS in viral propagation.

No.	Virus	Ubiquitinated protein	Ubiquitin acceptor sites/Ub-chain type	Roles of the ubiquitinated proteins in viral propagation	Refs
1	IAV	NP;	Lys184, Lys227, Lys273;	Facilitating viral replication;	[25–26];
		M2;	Lys78;	Enhancing IAV production;	[27];
		PB1	Lys48	cellular antiviral defence	[28]
2	DENV	NS1	Lys48	Regulation of NS1-NS4B interactions	[29]
3	CPXV	54 viral proteins	Lys(6, 11, 27, 29, 33, 48, 63)	Diverse roles in viral infection	[30]
4	ALV	Intergrase	Thr10, Cys37	Degradation signal	[31]
5	RSV	Gag	C-terminalglycine of Gag	Viral budding and release	[32]
6	HSV-1	Capsid	Lys48;	Viral genome release;	[36]
		IκBα	Lys48 (deubiquitination)	Immune evasion	[64]
7	Rotavirus	Unknown	Unknown	Enhancing viral replication	[38–39]
8	HTLV-1	Tax	Monoubiquitination	Transcriptional regulation	[40]
9	HIV-1	Tat	Lys(27, 29, 33)	Viral transcription;	[41]
		Gag	Unknown	Viral budding and release	[43]
10	HCV	NS2	Lys63	Viral envelopment	[42]
11	MCoV	Unknown	Unknown	Viral particle release	[44–45]
12	HAstV	Unknown	Unknown	Efficient replication	[47]
13	VACV	Unknown	Unknown	Viral replication	[48]
14	TBSV	P33	Lys70 and Lys76	Viral replication	[49]
15	HEV	Unknown	Unknown	Viral replication	[50–51]
16	PCV-2	Capsid	Unknown	Viral replication	[52]
17	EBOV	VP35	Lys309	Viral replication	[53]
18	PRRSV	NEMO	M1	Immune modulation	[66]
19	EBV	RIPK1/3	Lys63	Inhibition of host antiviral defences	[67]
20	HPV	E7	N-terminal residue of E7	Inhibitory growth of tumour	[70–71]

Note: IAV, influenza A virus; DENV, Dengue Virus; CPXV, cowpox virus; ALV, avian leukosis virus; RSV, Rous Sarcoma virus; HSV-1, herpes simplex virus type 1;HTLV-1, human T-cell leukaemia virus 1;HIV-1, human immunodeficiency virus type 1; HCV, hepatitis C virus; MCoV, murine coronavirus; VACV, vaccinia virus; TBSV, tombusvirus; HEV, Hepatitis E virus; PCV-2, porcine circovirus type 2; HAstV, human astrovirus; EBOV, Ebola Virus;EBV, Epstein-Barr virus; PRRSV, porcine reproductive and respiratory syndrome virus;HPV, human papillomavirus.

replication [59], and ubiquitinated Gag of RSV and human immunodeficiency virus 1 (HIV-1) contributes to viral budding and release [32, 42]. Meanwhile, Horan et al. reported that proteasomal degradation of Herpes simplex virus (HSV) capsids in macrophages releases viral DNA into the cytosol for recognition by DNA sensors [36]. In all, the UPS plays different roles during viral infection and propagation, as summarized in Table 1.

4. Viral immune evasion

Ubiquitination plays an important role in the regulation of host antiviral immune responses. The host innate immune response is the first line of defence against invading pathogens, and complex interplay exists between viruses and hosts to limit multiple steps of the viral life cycle. Some cellular proteins can function as restriction factors to limit viral infection by directly inhibiting viral replication or viral assembly. For example, polymerase PB1 of Influenza A virus (IAV) is ubiquitinated on K48 by the cellular E3 ubiquitin ligase TRIM32, and the resulting proteasomal degradation blocks viral replication [28]. However, some viruses have evolved strategies to avoid surveillance by the host immune system. Therefore, a dynamic balance between host immunological surveillance and viral immune evasion determines the success of viral propagation in host cells. An effective strategy for viral evasion of host immune surveillance is to target host immune adaptors and signalling molecules involved in proteasomal degradation. Early studies showed that human cytomegalovirus (HCMV)-encoded proteins US2 and US11 trigger the transfer of MHC class I molecules into the cytosol for ubiquitination and further degradation by the proteasome [60, 61]. Recently, some additional cellular targets of the HCMV US2 protein have been found to be ubiquitinated and degraded through the recruitment of the cellular E3 ligase (TRC8) [62], which contributes to prevent immune recognition of virally infected cells. Together, these findings demonstrate that HCMV has developed effective strategies to evade host immune responses via degradation of cellular targets.

It is generally accepted that the NF-κB pathway plays a critical role in host anti-viral defences [63], which contributes to enhance the resistance of hosts to infection by invading pathogens. However, viruses have evolved distinct mechanisms to modulate these host innate immune responses by the recruitment of the UPS. Some viruses such as herpes simplex virus type 1 (HSV-1), Varicella-zoster virus (VZV) and Simian varicella virus (SVV) are reported to inhibit the activation of host innate immunity by the UPS, thereby leading to escape from host immune responses [64, 65]. For example, Ye et al. reported that UL36USP deubiquitinates IκBα and limits its degradation, resulting in the evasion of host antiviral innate immunity through abrogation of NF-κB activation [64]. Furthermore, recent research showed that the protein encoded by ORF61 in SVV and VZV prevents ubiquitination and degradation of IκBα, thereby suppressing NF-κB-mediated immune responses [65]. Moreover, Jing et al. reported that reproductive and respiratory syndrome virus (PRRSV) nsp1α inhibits NF-κB activation by targeting the linear ubiquitin chain assembly complex [66]. It resulted in the reduction of the linear ubiquitin chain assembly complex dependent linear ubiquitination of NF-κB essential modulator (NEMO), revealing an additional mechanism of immune modulation by PRRSV [66]. Additionally, some viruses such as HSV and cytomegalovirus have evolved mechanisms that inhibit necroptosis to overcome host antiviral defences. For example, Liu et al. reported that latent membrane protein 1 of Epstein-Barr virus suppresses necroptosis to overcome host antiviral defences by targeting RIPK1/3 ubiquitination [67]. These mechanisms of viral immune evasion developed by viruses contribute to establishing and maintaining infection and viral pathogenesis in host cells.

5. Degradation of cellular proteins by the UPS during viral infection

Until recently, the UPS and autophagy were considered to be largely independent systems targeting proteins for degradation in the proteasome and lysosome, respectively. The majority of cellular misfolded proteins, including some viral proteins, are degraded by the UPS, in which Ub-tagged substrates are deubiquitinated, unfolded and cleaved into small peptides when passing through the narrow chamber of the

proteasome. The degradation of viral proteins not only alleviates the survival pressure of host cells, but also provides recycled peptides for the synthesis of cellular proteins. Ubiquitination serves to target proteins for proteasomal degradation, and viruses modulate this system to assist replication and to escape host immune responses. Many viral proteins, such as the DENV capsid protein [59], HIV-1 Gag protein [68] and the PCV-2 capsid protein [69], are ubiquitinated and further degraded by the UPS. The degradation of viral capsids facilitates the transfer of the viral genome into host cells for the expression of viral genes. For example, Byk et al. reported that the degradation of capsid by the UPS is required for the initial rounds of DENV translation [59]. A recent study showed that the ubiquitination and degradation of the PCV2 capsid protein mediated by Makorin ring finger protein 1 can modulate replication and pathogenesis in targeted tissues [69]. Moreover, some viral proteins such as HPV E7 [70, 71], tobacco mosaic virus movement protein and HCV NS2 are ubiquitinated and further degraded by the UPS [72, 73], and ubiquitination of the N-terminal residue of HPV E7 contributes to inhibition of tumour growth.

Additionally, some cellular restriction factors are degraded by the host UPS, but this can be subverted by some viruses to facilitate viral propagation. In this respect, the human immunodeficiency viruses (HIV-1 and 2) represent excellent examples. For example, the HIV accessory proteins Vif, Vpx and Vpu can hijack the UPS to exert their counter defence [54]. Some viruses can recruit cellular E3 ligases to target anti-viral proteins for degradation. For example, the HPV E6 protein binds to the cellular E3 ligase E6-associated protein (E6AP) to form an E3 complex to mediate p53 degradation [74]. Similarly, the HPV E7 protein targets a tumour suppressor protein and retinoblastoma protein to modify proteasomal degradation mediated through a cullin E3 complex [75]. Moreover, some viruses were reported to encode their own E3 ligases, as is the case for Kaposi sarcoma herpesvirus protein K3, K5 and HSV-1 ICP0, which mediate the degradation of host proteins [76–78]. This degradation of anti-viral proteins strongly facilitates viral replication and propagation in host cells.

6. Conclusions and future studies

As mentioned above, the UPS plays significant roles in the regulation of viral replication and propagation in host cells. Moreover, ubiquitination can also affect protein-protein interactions, DNA repair, localization and trafficking, signal transduction, apoptosis and cell cycle regulation [79, 80]. In fact, ubiquitination and other forms of modification such as phosphorylation provide countless opportunities to modulate almost all known biological processes. Accumulating evidence suggests that viruses interact with the UPS to regulate interactions with hosts and at multiple levels (see Table 1). The UPS functions as a form of host defence machinery to eliminate invading pathogens, but many viruses can manipulate the UPS to their advantage in various ways, thereby facilitating viral propagation in host cells. Taken together, the above studies demonstrate that in the continuous battle between viruses and host cells, viruses have evolved distinct mechanisms to degrade host restriction factors and evade host innate immunity to facilitate viral propagation. In many cases, these mechanisms work together to dynamically regulate the function of the UPS to facilitate viral infection.

As described above, the UPS is very important for allowing many viruses to accomplish their life cycle. Therefore, a better understanding of the complicated interactions between viruses and the host UPS could assist the identification of new therapeutic targets. However, the roles of the UPS in some insect viruses such as *Bombyx mori* nucleopolyhedrovirus (BmNPV) and *Bombyx mori* bidensovirus (BmBDV) has not yet been reported. These two viruses specifically infect silkworm, resulting in flacherie infection that causes significant economic damage to silkworm farmers. Therefore, elucidating the roles of the UPS in the BmNPV and BmBDV life cycle will form the basis of future work in our group, and this could lead to the identification of novel targets for blocking virus invasion and replication. Furthermore, characterization of ubiquitin modification and degradation events in silkworm will likely provide novel insight into the mechanisms of viral pathogenesis, facilitate the discovery of new immune modulators, and promote the development of efficient antiviral interventions.

Conflict of interest

The authors have declared no conflict of interest.

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