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Viruses and sumoylation: recent highlights

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Since its discovery in 1997, SUMO (small ubiquitin-like modifier) has been implicated in a range of activities, indicating that this protein is as important in the cell as ubiquitin is. Although it can function throughout the cell, it appears to be involved more in nuclear functions. The growing list of substrates that are covalently modified by SUMO includes many viral proteins; SUMO appears to facilitate viral infection of cells, making it a possible target for antiviral therapies. It therefore is important to understand how viruses manipulate the cellular sumoylation system and how sumoylation affects viral functions.

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Introduction

Sumoylation is emerging as a central theme in protein function regulation. As such, it is no surprise that viral proteins were among the first to exploit the host SUMO system. In regard to viruses and their exploitation of sumoylation, two possible scenarios can be envisioned: a viral protein that influences sumoylation, and/or a viral protein that needs to be sumoylated in order to exert its function. One type of virus–host interaction that is well established and widespread is the modulation of viral protein function by post-translational modification systems, which include sumoylation.

SUMO (small ubiquitin-like modifier) modification induces proteins to change their localization, the interaction with their partners or cellular components, or their stability and enzymatic activity. However, viruses have evolved numerous mechanisms to overcome host defenses and to use host biochemical pathways for their benefit.

The 11 kDa SUMO moiety is covalently attached to the ε-amino group of the lysine residues of its target proteins through four enzymatic reactions. First, SUMO proteins are post-translationally processed by SUMO proteases to expose a COOH-terminal diglycine motif, which can then form a thioester bond with the catalytic cysteine of the E1-activating enzyme, the SAE1/SAE2 (SUMO activating enzyme) heterodimer. Second, this activation step is followed by conjugation of the activated SUMO to the E2-conjugating enzyme UBC9 (ubiquitin-conjugating enzyme) through the formation of another thioester bond. Finally, through the mutual action of UBC9 and E3 SUMO ligases, SUMO is bound to its target on a lysine residue, by an isopeptide bond. The system is dynamic and reversible by isopeptidases, which can hydrolyze this covalent bond, causing the removal of SUMO, which can then cycle again (Figure 1) [1,2,3•,4•].

Viral interference with the sumoylation of host proteins could be accomplished by preventing *de novo* sumoylation, by enhancing desumoylation or by using SUMO for viral benefit, as long as the outcome is an environment that is more favorable for viral propagation.

As sumoylation is a multi-step reaction, a viral protein could inhibit conjugation at a number of points. Alternative modes of inhibition include interference with E1–SUMO thioester formation, transfer of SUMO from E1 to E2 or transfer of SUMO from E2 to substrate. Recent work from our laboratory has resulted in the publication of the first example of a viral protein, Gam1, that binds to the E1 heterodimer, inhibiting its function and causing a complete block of the sumoylation pathway both *in vivo* and *in vitro* [5]. Gam1 is an avian adenoviral protein that we have been focusing on as a model for the study of viral interference with cellular pathways [5–10].

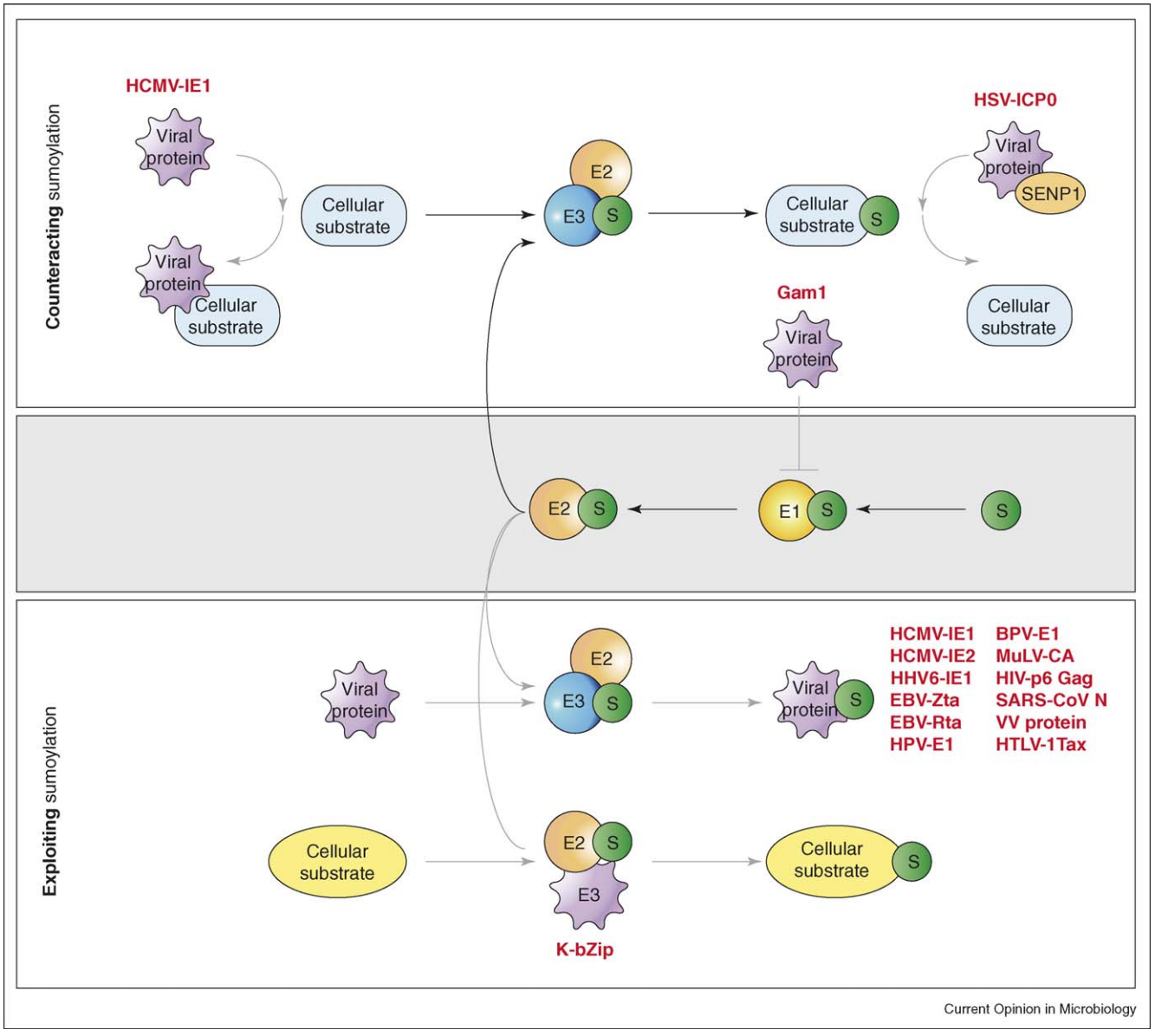
The latest on viral proteins and SUMO

In recent years a plethora of data has emerged concerning various viruses and their interaction with the sumoylation machinery. The most recent literature on the interplay between viruses and the various components of the SUMO pathway, with an emphasis on data published in the past two years is highlighted here. Although four SUMO paralogs have been found in vertebrates, the paralog that viruses appear to prefer is SUMO-1; therefore, throughout this review, SUMO-1 is referred to as SUMO.

Herpesviridae: human cytomegalovirus and herpes simplex virus

The viral proteins that interact in some way with SUMO are generally encoded by DNA viruses that replicate in the nucleus, and if the sumoylation of these proteins is

Figure 1



The viral proteins discussed in this review and their interaction with the SUMO pathway. The upper panel shows how viral proteins could counteract the host's sumoylation, either by preventing *de novo* sumoylation (HCMV-IE1), by enhancing de-sumoylation (HSV-ICP0) or by inhibiting the sumoylation enzymatic cascade (Gam1; middle panel). Some viral proteins could exploit the host's sumoylation because they need to be SUMO-modified in order to exert their functions (lower panel). Abbreviations: S, SUMO; E1, SUMO-activating enzyme (SAE1/SAE2); E2, SUMO-conjugating enzyme (UBC9); E3, SUMO-ligases.

interfered with, this disrupts the localization of the proteins to the nucleus. Among the DNA viruses, all of the known sumoylated viral proteins are immediate-early or early nuclear proteins. An initial connection between virus infection and sumoylation was observed for the herpes simplex virus (HSV) immediate-early protein ICP0 (infected cell protein 0) [11,12].

Subsequently, a study aimed at determining whether the human cytomegalovirus (HCMV)-induced dispersion of promyleocytic leukemia nuclear bodies (PML NBs) involved SUMO discovered the first viral protein found to be sumoylated: immediate-early 1 protein (IE1) [13]. PML NBs are sub-nuclear complex structures, with no unique defined role, that become disrupted during infection by most DNA viruses. The exact role of the disruption of PML NBs by the regulatory proteins of DNA viruses is still not clear. However, the importance of their disruption at very early stages of virus infection has been suggested by a number of findings [3•].

The HCMV-IE1 72 kDa protein is a regulator of early events in the lytic infectious cycle, and the functions of this protein are also controlled by post-translational modifications. Two recent studies have given a slightly different twist to the role of sumoylation for this immediate-early viral protein [14,15]. In the attempt to assess the role of SUMO for this particular protein, the authors created a recombinant virus that is mutated in the SUMO–IE1 attachment lysine residue and studied the phenotypic consequences of this mutation [15]. They showed that SUMO modification is not absolutely required for productive viral infection, but clearly contributes to full activity of E1. This evidence suggests that the non-conjugated and SUMO-conjugated forms of IE1 might perform distinct functions during virus infection. Indeed, lack of sumoylation did not affect the ability of IE1 to reach the nucleus, disrupt PML bodies or bind chromatin. However, sumoylation of IE1 did contribute to efficient HCMV replication by promoting the expression of IE2, the principal transcriptional activator of the HCMV lytic cycle; therefore, the former most abundant non-conjugated isoform might facilitate expression of early viral genes and viral replication by promoting SUMO-independent activities, whereas the SUMO-conjugated variant supports efficient lytic viral growth.

What about the effects of HCMV on sumoylated targets? Studies have suggested that modification of PML by SUMO is essential to form NBs, and essential for the maintenance of their integrity. IE1 binds to PML and prevents or removes SUMO adducts from it. Lee *et al.* [14] have now shown that the ability of HCMV-IE1 protein to modulate sumoylation of PML correlates with its functional activities in transcriptional regulation and infectivity. In fact, the activity of IE1 in the regulation of transcription directly correlated with its ability to bind to and to desumoylate PML, thereby disrupting PML NBs. This study also confirms that HCMV and HSV type 1 (HSV-1) seem to use different mechanisms to desumoylate PML. Specifically, the disruption of NBs by HSV-1 ICP0 — which itself has an intrinsic ubiquitin E3 ligase activity — was prevented by the addition of the proteasome inhibitor MG132 (carbobenzoxy-L-leucyl-L-leucinal; Z-LLL-CHO). On the contrary, HCMV IE1 interferes with sumoylation of PML in a proteasome-independent manner [14].

How the HSV-1 regulatory protein ICP0 reduces sumoylation of PML and other substrates, however, is still partly uncertain; although exogenously expressed SUMO protease SENP1 (sentrin/SUMO-specific protease) only colocalizes with PML NBs in the presence of ICP0 during natural HSV infection [16]. This also remains an attractive model for other viral proteins, but additional studies are required to confirm whether endogenous proteases can be recruited to these structures by viruses, thereby promoting desumoylation. For example, this is not the case for Gam1: work from our laboratory has undoubtedly excluded the possibility that Gam1 inhibits sumoylation by recruitment of SUMO proteases activities [5].

SUMO and transcription

Two common themes arise: one is that viral transcriptional regulators are modified by SUMO; the other is that many viruses might use the SUMO system for localization of their regulatory proteins near or inside the nuclear membrane of infected host cells; mammalian RanGap is bound to the nuclear pore complex by a mechanism that involves SUMO [4].

Generally, SUMO-modification is gaining acceptance as a mechanism of repression of the transcriptional activation potency of transcriptional factors, although in a limited number of instances it correlates with an increase in transcriptional activity [2,17]. Consistent with this, one of the most recent examples reported in the literature is the Kaposi's sarcoma-associated herpesvirus' (KSHV) early lytic-cycle, K-bZIP (KSHV basic leucine zipper protein). K-bZIP repression activity correlates with its ability to be sumoylated and to recruit UBC9 to specific viral target promoters, exerting this protein's transcriptional repression activity [18••]. One attractive hypothesis suggested by the authors is that K-bZIP functions like a SUMO ligase or a SUMO E3 adaptor, localizing UBC9 with its potential substrates and modifying the chromatin structure surrounding the transcriptional complex where K-bZIP resides. K-bZIP therefore joins the list of sumoylated herpesvirus immediate-early proteins, which include HCMV IE1 and IE2, Epstein-Barr virus (EBV) Zta and Rta, and human herpes virus-6 (HHV6)-IE1 [3•].

An unresolved issue still remains for sumoylated HHV6-IE1, where no clear function for SUMO has yet been provided [19,20]. Sumoylation of the different variant forms of HHV6-IE1 did not seem to influence its trans-activating potential, or its ability to target PML NBs; therefore, at present the functional consequences of sumoylation of this protein is still undetermined.

EBV is usually maintained under latent conditions in B lymphocytes, and to proliferate it must enter the lytic cycle, during which the virus expresses two immediate-early proteins, Rta and Zta, to activate viral early genes and the lytic cascade. EBV Zta was shown to be modified by SUMO and to disperse PML NBs, perhaps by outcompeting PML for a limited amount of intracellular SUMO [21]. Furthermore, in reporter assays, SUMO inhibited Zta trans-activation of both the EBV BMRF1 and Rta promoters, but had no effect on Rta trans-activation activity [22]. Chang *et al.* [23] instead showed the EBV Rta protein to be SUMO-modified and that this modification increases the trans-activation activity of Rta. This discrepancy is probably associated with the promoters selected in each study, or because different cell lines were used. Nevertheless, the different effects of SUMO

modification on trans-activation properties of immediate-early proteins from the same virus could be a way of enabling the virus to fine-tune viral trans-activation activities. Another example of a herpesvirus protein transcription factor enhanced by sumoylation is HCMV-IE2. HCMV-IE2 appears to have a major role in promoting the replicative cycle for HCMV, by exerting two well-defined activities during infection: first, it acts as a powerful non-specific trans-activator of both early viral and cellular genes; and second, it acts as a transcriptional repressor of its own promoter [3•,24]. There is now evidence that HCMV-IE2 is covalently modified by SUMO, and this modification appears to be required for trans-activation function of this IE2 [25,26], further supported by data showing a correlation between its trans-activation activity and sumoylation level [27]. However, sumoylation of HCMV-IE2 is not required for virus growth in cultured human fibroblasts [28], leaving the still-open question as to whether sumoylation of HCMV-IE2 plays a role in viral infection. HCMV-IE2 was also found to be the first viral target regulated by a SUMO E3 ligase [29]. In fact, the SUMO E3 ligase PIAS1 (protein inhibitor of activated STAT [signal transducer and activator of transcription] 1) stimulates conjugation of SUMO to IE2, similarly to Rta protein of EBV [23]. These are two examples of immediate-early viral proteins where the role of SUMO is to enhance their trans-activation activities. Interestingly, PIAS1 is the only SUMO E3 ligase found to date to enhance sumoylation of viral proteins. Briefly, three classes of mammalian E3 ligases have been found [4•], but their substrate-specificity and to what extent the substrate-specificity of these SUMO E3 ligases overlap is still unknown.

SUMO and papilloma viruses

Another example of a viral protein, the sumoylation of which is enhanced by PIAS family, is the papillomavirus (PV) E1 protein [30]. In both adenovirus type 5 and PVs, sumoylation is important for nuclear targeting of their early proteins. The PV E1 protein plays a crucial role during infections and both human PV and bovine PV E1 proteins are SUMO-modified, a key determinant for the nuclear localization of the protein [31,32]. Therefore, modulating E1 sumoylation might be one of the factors that regulates the outcome of a PV infection. The study by Rosas-Acosta *et al.* [30] indicate that PIAS proteins are possible modulators of PV E1 sumoylation during PV infection.

One area of potential interest is the link between sumoylation and differentiation in various systems. This idea was very recently strengthen by a study aimed at investigating the mechanism by which sumoylated MEF2A (transcription factor myocyte enhancer factor 2A) promotes dendritic claw differentiation [33••]. In the same line of thought, PV infections are characterized by tightly controlled synchronization events between replication of the viral genome, production of new infectious virus and the differentiation of its keratinocyte host cell [34]. Therefore studies aimed at elucidating the role of the sumoylation system during keratinocyte differentiation might help in understanding of the biological role of sumoylation during PV infections.

More and more

In the past two years a small discovery has been made for two retroviruses. Recent studies with chimeric viruses containing different regions of the viral Gag genes of Moloney murine leukemia virus (MuLV) and HIV type 1 (HIV-1) have suggested that the Gag capsid (CA) protein is a dominant determinant of retrovirus infectivity [35]. Interestingly, a binding site in the CA for both UBC9 and PIASy was found and mapped in Moloney MuLV [36]. CA sumoylation was required for formation of the nuclear viral DNA forms and for viral replication [36]. Furthermore, the p6 Gag of HIV-1 has recently been shown to be modified by SUMO [37]. Although mutation of this residue had no apparent effect on virus replication, overproduction of SUMO decreased HIV-1 virion infectivity, and the non-sumoylated mutant virus was resistant to this effect, suggesting that SUMO modification of HIV-1 p6 regulates HIV-1 infectivity [37]. HIV-1 expresses several regulatory proteins, which allow efficient production of viral particles. Particular focus has been given to two of them, Tat and Rev, because the functions they exert are necessary to viral replication. As a note of interest, Tat has been recently shown as a modulator of cellular protein ubiquitination [38•]. A report has demonstrated how HIV-1 replication can be inhibited by using peptides that target Rev [39]. Association of these peptides with SUMO for their stabilizations enabled them to efficiently penetrate within lymphocytes and, in some cases, inhibit the function of Rev [39].

SARS (severe acute respiratory system) coronavirus (SARS-CoV) N protein also undergoes sumoylation, with some indication that this modification might play an important regulatory role in the SARS-CoV replication cycles [40].

The poxvirus vaccinia (VV) is another recent example of how a viral protein can use SUMO. Quantitative SUMO modification of a VV protein is required for its successful localization to the viral cytoplasmic 'mini-nuclei' and prevents self-association of the protein, providing the first case of a DNA virus for which sumoylation is a prerequisite for its localization to cytoplasmic entities [41•]. This is novel, because all other viral proteins modified by SUMO are encoded by DNA viruses that replicate in the nucleus and require SUMO for their correct nuclear localization.

Finally, an interesting and novel interaction between a geminivirus replication protein and the plant sumoylation system was published recently [42]. Effects on geminivirus

replication were observed in transgenic plants with both positive and negative changes in SUMO levels [42].

Ubiquitination and sumoylation

The transcription factor nuclear factor κB (NF-κB) and its activator IκB kinase (IKK) operate as an evolutionarily conserved element that allows cells to adapt to environmental changes. In other types of cancers, NF-κB is crucial for the induction of adult T-cell leukemia, which is linked to infection by human T-cell leukemia virus type 1 (HTLV-1). The HTLV-1 regulatory protein is Tax, a potent transcriptional activator with oncogenic potential, in part because of its ability to activate the NF-κB pathway. Tax activation of the NF-κB pathway involves its interaction with the regulatory subunit of the IKK complex, NF-κB essential modulator (NEMO)–IKKγ. A recent report has shown that Tax is sumoylated and ubiquitinated on overlapping lysine residues, determining then the partitioning of Tax in the nuclear and cytoplasmic compartments [43••]. Tax only co-localized with ubiquitin and IKK complexes in the cytoplasm, followed by the translocation of the RelA subunit of NF-κB into the nucleus. Deubiquitinated Tax then migrates to the nucleus, where it becomes sumoylated and is able to assemble NBs that contain both Rel A and IKKγ, leading to the activation of specific Tax-responsive genes. Desumoylated Tax can then exit the nucleus [43••]. Thus, both modifications are crucial for Tax-mediated transcriptional activity, and might result in targets for treatment of adult T-cell leukemia.

Conclusions

It is clear that SUMO is important for viruses and although putative functions have been attributed to sumoylation, the precise biological role played by this process in terms of viral fitness remains to be determined. This scenario has become complicated owing to most recent emerging ideas, which support evidence for non-covalent interactions with SUMO. Briefly, SUMO-like proteins have been studied mainly in the context of their covalent conjugation to target proteins. However, data is now pointing towards the possibility that proteins containing SUMO-interacting motifs can non-covalently interact with SUMO, without necessarily being modified by SUMO [44,45]. Among viruses, a few known examples include the nucleocapsid proteins from two hantaviruses and a retroviral Gag protein [3•]. Most recently EBV nuclear antigen 3C has been described as containing such a SUMO-associating domain, necessary for transcriptional activation [46]. Taken together, this data implies a possible novel mechanism of binding target sequences by SUMO through a SUMO-binding motif, with the consequence of providing another level of control for SUMO over its targets.

To understand this system better will be the challenge of future research, because sumoylation might be a pathway to target with antiviral inhibitors.

Update

Recently, several studies describing viral mechanisms for manipulating signalling pathways in the host were published: we encourage our readers to read these [47–54].

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