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1 **Viral hijacking of cellular ubiquitination pathways as anti-innate immunity strategy**

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10
11 **Running Head:** Viral hijacking of ubiquitination

12
13
14 **Abbreviations:**

15 APOBEC, apolipoprotein B mRNA-editing enzyme C; APC/C, anaphase promoting
16 complex/cyclosome complex; DDB1, UV-damaged DNA binding; DNA-PK, DNA protein kinase;
17 DUBs, deubiquitinating; E6-AP, E6-associated protein; Hdlg, human homology of the Drosophila
18 melanogaster discs large; HECT, homology to the E6-associated protein carboxyl terminus; HPV,
19 human papilloma virus; hScrib, human homology of the Drosophila scribble; hTERT, the catalytic
20 and rate-limiting subunit of telomerase; ICP0, infected cell protein 0; IFN, interferon; ISG,
21 interferon stimulated gene; KSHV, Kaposi sarcoma associated herpesvirus; MIR1/MIR2,
22 modulator of immune recognition; PHD, plant homeodomain; PML, promyelocytic leukaemia
23 antigen; pRB, retinoblastoma protein; RING, really interesting new gene; SCF, Skp1/Cullin1/F-
24 box; Ub, Ubiquitin; Ubc, ubiquitin conjugating; USP7, ubiquitin-specific protease enzyme; VIF,
25 viral infectivity factor.

26
27 **Abstract:**

28
29 Viruses are obligate parasites of host cells. The virus/host coevolution has selected virus for
30 growth despite antiviral defences set up by hosting cells and organisms. Ubiquitin conjugation
31 onto proteins, through a cascade of reaction mediated by the E1 ubiquitin activating enzyme, E2
32 and E3 ubiquitin conjugating ligases, is one of the major regulatory system which, in particular,
33 tightly control the concentration of cellular proteins by sorting them for degradation. The
34 combined diversity of E2 and E3 ligases ensures the selective/specific ubiquitination of a large
35 number of protein substrates within the cell interior. Therefore it is not surprising that several
36 viruses are coding proteins with E3 ubiquitin ligase activities to target cellular proteins which play
37 a key role in the innate antiviral mechanisms.

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41 77 87 54.

42 Introduction

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45 Viruses have evolved to sneak through the innate and adaptive antiviral response both at
46 the cellular and whole organism levels, for survival and successful infection spreading (29, 38,
47 57). Most aspects of the life cycle of viruses critically rely on the specific interaction between viral
48 and host cell proteins to redirect the cellular metabolism for their benefit. Post-translationally
49 polypeptide tagging by the conjugation of ubiquitin (ubiquitination), sumo (sumoylation), Nedd8
50 (neddylation) and ISG15 (ISGylation) (52, 124) is a potent way to alter protein function and/or to
51 sort protein. The ubiquitin-proteasome system is a mandatory player in many regulatory
52 processes in mammalian cells (39). Monoubiquitination of proteins are sorted and
53 polyubiquitinated proteins are targeted for degradation into small peptides by the 26S proteasome.
54 The latter is necessary to ensure efficient turn-over of most cellular proteins. Elegantly, the
55 evolution has selected for the screening of short peptides derived from proteasome degradation
56 as a read-out of self integrity via the MHC class I presentation pathway to CD8 T lymphocytes.

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Ubiquitin (Ub) is a conserved 76 amino acid polypeptide when attached to a protein
mediates interaction with other proteins (53). Ubiquitin conjugation to a substrate involves a
cascade of at least three different enzymatic reactions. In the first step, the ubiquitin binds to the
C-terminus of E1 activating enzyme by a thioester linkage through an energy-requiring process.
In the second step, activated Ub is transferred, again through a thioester linkage, to an ubiquitin
conjugating enzyme E2 (Ubc) or E2 ligase. In the third step, the activated ubiquitin is transferred
from the E2 thioester linkage to a lysine residue of the target protein, through a peptide-bond onto
the side chain, resulting in a branched peptide. This last step is catalyzed by an Ubc E3 or E3
ligase, which specifically recognizes the substrate proteins. Ubiquitination can reversibly take
place through the action of deubiquitinating (DUBs) enzymes, which remove ubiquitin chains from
specific ubiquitin-protein conjugates (5, 23, 53, 124). Thus ubiquitination follows dynamic forward
and backward processes. In human, the Ub enzymatic players are unique for E1, over 50 for E2
and several hundreds for E3. The large number of E2 and E3 ligases and their combination
ensures the necessary specific and individual targeting of thousands of different proteins.

Structurally and functionally, E3 ligases are heterogeneous. One group, which includes
the Nedd4 family, is characterized by the presence of the homology to the E6-associated protein
carboxyl terminus (HECT) catalytic domain, (58). These are the only catalytic E3 ligases on which
activated Ub is transferred from E2, again through a thioester bond, before Ubiquitin transfer to
the target substrate through a peptide bond. The prototype is the E6-associated protein (E6-AP).
The second group acts only as a linker or a scaffold to bring specific substrates near Ub charged
E2 ligase closer enough to enable the Ub transfer from E2 to a Lys residue of the substrate. This
group can be subdivided into unimolecular and multimolecular E3 ligases. Unimolecular linker-
type E3 ligases contain a Zn-finger called the really interesting new gene (RING) domain which
recruits E2 enzymes. RING domains are closely related to PHD domains (or PHD fingers) and
the frontier is disputed among the structuralists, the issue of which is the prediction of E3 ligase
activity (109). The U-box is found as an alternative to the RING domain. U-box is predicted to be
structurally related, but lack the hallmark metal-chelating residues (50). The prototype of
unimolecular RING E3 ligase is MDM2, the major E3 ligase of p53. The multicomponent E3
ligases contain a variable number of subunits with at least one subunit characterised by the
presence of a RING domain and a complex containing one Cullin protein. The RING domain is
responsible for the recruitment of E2 and the Cullin complex acts as a scaffold for the recognition
of specific substrates. Prototypes of multisubunit E3 ligases are the SCF (4) and anaphase
promoting complex/cyclosome (APC/C) complex (17).

Because of the necessary continuous adaptation of viruses to their hosts, it is not
surprising that viruses can modify the ubiquitin-proteasome machinery of host cells and use it for
their own profit. So far, this modulation process takes place at the E3 ligase level i.e. at the step
where the substrate specificity is critically defined. Some viral proteins acts as E3 ligases, and
other redirect host ubiquitin E3 ligases to target new substrate proteins (5). Viral E3 ligases are
involved in the regulation of many aspects of viral and cellular processes such as virus budding,
cell division, apoptosis, antigen presentation, lymphocyte activation, induction of T cell-tolerance,
immune evasion, and innate immunity to list a few (5, 75).

98 The scope of this review is to focus on viral hijacking of Ubiquitin ligases to modulate
 99 cellular intrinsic antiviral activities and innate immunity. Based on a classification of E3 ligase
 100 according to their catalytic/non catalytic activity, and on their unimolecular or multisubunit
 101 structure, the following viral ubiquitin E3 ligases will be reviewed: RTA, a novel unimolecular
 102 catalytic E3 ligase, E6, a E3 ligase able to hijack another (catalytic) E3 ligase, ICP0 a
 103 bifunctional unimolecular RING-type E3 ligase, E4orf6/E1B55K and VIF, two RING/Cullin E3
 104 ligase “BC-box” subunits, and V, a RING/Cullin E3 ligase subunit with a new Zn-finger motif.

106 107 **1) Kaposi sarcoma associated herpesvirus RTA protein: an unimolecular viral catalytic E3** 108 **ligase**

109
110 Kaposi sarcoma associated herpesvirus, KSHV, is a DNA tumour virus that cause rare
 111 endothelial and lymphoid tumour mostly in immunocompromised patients. The viral RTA protein
 112 is a DNA binding nuclear transcription factor acting throughout the virus replication cycle.

113 114 **Gene and structure**

115 KSHV Orf50 codes an protein of 691 amino acid length, called RTA, which is a homolog
 116 of the RTA protein coded by Epstein Barr virus, another oncogenic *herpesviridae* (116). It was
 117 found to bind to IRF7 during a yeast two hybrid screening of a human cDNA library.

118 119 **E3 ligase activities**

120 RTA amino-terminal half-part binds to IRF7 (FIGURE 1) and induces its polyubiquitination
 121 and degradation by the proteasome. In vitro, RTA acts as a unimolecular E3 ligase for
 122 ubiquitination of IRF7 in the presence of the Ubch5 α E2 ligase, E1 and ubiquitin. RTA also
 123 recognises itself as a substrate for polyubiquitination. RTA has a Cys-rich region of a novel type
 124 which is proposed to harbour the intrinsic catalytic E3 ligase activity. Indeed mutations of key Cys
 125 or His residues within this region result in the loss of E3 ligase activity of RTA without hampering
 126 its binding to IRF7 (127).

127 128 **Cellular impact and counteraction of innate immunity**

129 Besides the key role of RTA in the positive regulation of viral transcription (see (127) and
 130 references therein), RTA is predicted to counteract the innate immunity by preventing the
 131 activation of IFN- α gene. Indeed IRF7 is a key transactivator of this gene (95). Interestingly,
 132 KSHV code for at least two other proteins with E3 ligase activity, MIR1 and MIR2. They are
 133 involved in the regulation of the adaptative immunity, because they target MHC class I molecules
 134 for degradation (24).

135 136 137 **2) Human papillomavirus E6 protein: hijacker of a unimolecular E3 ligase**

138
139 The high risk human papillomaviruses (e.g. HPV-16 and HPV-18) are causative agents of
 140 cervical cancers. Their oncogenic properties correlate with the transforming activities of the viral
 141 oncogenes E6 and E7. Both of them use the ubiquitin-proteasome system to target a variety of
 142 important negative cell regulatory proteins. E7 protein upregulates proliferation-related genes by
 143 interacting with the retinoblastoma protein pRb, and related protein p107 et p130 (31), (see also
 144 (5, 110) for review). E6 circumvents the cell apoptotic response to uncontrolled cell proliferation
 145 by binding to p53 (123), see also (67) for review.

146 147 **Genes and structures**

148 E6 and E7 are two early transcribed genes located first after the unique viral transcription
 149 promoter. E6 and E7 are relatively small proteins with a size of about one hundred and one
 150 hundred and fifty amino acids, respectively. Non oncogenic HPVs differ from the oncogenic HPV-
 151 16 and HPV18 by encoding E6 and E7 proteins poorly efficient in recruiting their cellular targets
 152 for degradation by the ubiquitin and proteasome pathway (26, 41, 107).

153

154 **E3 ligase activities**

155 E6 protein displays two types of E3 ligase activities according to the involvement or not of
156 the cellular E6-AP protein (FIGURE 2).

157 *E6-AP dependent E3 ligase*

158 On one hand, E6 binds through its N-terminus to the unimolecular E6-AP E3 ligase. E6-
159 AP contains an active enzymatic HECT site which interacts with several E2 conjugating enzymes,
160 including UbcH5, UbcH6, UbcH7 and UbcH8 (see (110) for review). On the other hand, E6
161 recruits many cellular proteins as substrates for ubiquitination.

162 E6 oncoprotein promotes the degradation of p53 through its interaction with E6-AP to
163 form an E3 ubiquitin ligase complex (55, 117) (see also (110) for review). Firstly, E6 associates
164 with E6-AP, secondly, the dimeric E6/E6-AP complex binds to p53 and induces E6-AP-mediated
165 ubiquitination of p53, and thirdly, polyubiquitinated p53 is recognized and degraded by 26S
166 proteasome (see (110) for review). E6 association with E6-AP likely alters its substrate specificity
167 because E6-AP itself is unable to recognize p53 as a target for ubiquitination (117). Conversely,
168 does E6 binding to E6-AP prevent its activity on normally E6-independent substrates ? The
169 precise scaffold of the E6/E6-AP/p53 complex is yet to be uncovered. It is proposed that a small
170 helical domain within E6-AP (L2G motif), which binds to E6, also associates with p53 (56), and
171 E6 binds to the core DNA-binding domain of p53 (44, 96). Strikingly, the effect of E6 on p53 is
172 independent of the six C-terminal lysine residues in p53, which are critical for effective
173 ubiquitination mediated by the physiological cellular unimolecular RING-type E3 ligase Mdm2
174 (15).

175 HPV E6 proteins also promote the E6-AP-dependent degradation of many other proteins
176 (see (37, 110) for review) that are independent of p53 degradation, including E6-AP (59), the
177 human homolog of the *Drosophila melanogaster* tumor suppressor Discs large (hDLG), the
178 human homolog of the *Drosophila* Scribble (Vartul), the apoptosis-promoting Bak protein, a novel
179 GAP protein called E6TP1, MAG-1, the DNA repair protein, O(6)-methylguanine-DNA
180 methyltransferase MGMT, MUPP-1, the GAIP(GTPase-activating protein for G α l)- interacting
181 protein C terminus TIP2/GIPC (36) and two PDZ containing proteins, hScrib, a tumor suppressor
182 protein, and NFX1-91, a cellular repressor of human *hTERT* (the catalytic and rate-limiting
183 subunit of telomerase) (72). E6 also binds to, and can ubiquitinate c-Myc (42), although this latter
184 event is not observed in physiological conditions (122).

185 *E6-AP independent E3 ligase*

186 E6 is also an E3 ligase in the absence of E6-AP for several substrates including Blk, a
187 member of the Src-family of non-receptor tyrosine kinase, Bak, a human proapoptotic protein,
188 Mcm7 and two human homologues of the yeast DNA repair protein RAD23, HHR23A and
189 HHR23B. The mechanism by which E6 targets proteins for degradation in an E6-AP-independent
190 manner is presently **unclear** (see (5, 110) for review).

191 *Cellular partners but not substrates of E3 ligase*

192 E6 interacts with another set of cellular proteins without evidence for ubiquitination and
193 degradation including E6-BP (21), CBP/p300 (94, 130), Tyk2 (65), the transcriptional integrator of
194 the E2F1/DP1/RB cell-cycle regulatory pathway TRIP-Br1 (45) and IRF-3 (103). The binding site
195 of these partners are unknown, but there is evidence for multiple binding sites on P6 including its
196 PDZ binding domain.

197 *E7 protein: a substrate recruiting sub-unit of an E3 ligase?*

198 The ability of oncogenic HPVs to target cellular proteins for proteasome-mediated
199 degradation is not restricted to E6. E7 is a substrate for the UbcH7 E2 and Cul1-Skp2 containing
200 E3 ligases (89). E7 binds to pRb and related proteins (5, 110) and induces their ubiquitination and
201 degradation by the 26S proteasome. These data suggest that E7 may also act as a substrate
202 recruiting sub-unit of a complex E3 ligase.

203

204 **Cellular impact and counteraction of innate immunity**

205 Besides their strong impact on the cell cycle control, apoptosis and oncogenic properties
206 which are the subject of intensive work, E6 and E7 proteins exhibit multiple anti-interferon
207 activities (62). Surprisingly the inhibitory effect of E6 and E7 is not related with their ability to
208 target cellular protein for ubiquitination and degradation. E6 binds to CBP, P300 and IRF-3 and
209 inhibits their transcriptional activity (94, 103). Since IRF3 and CBP/p300 are cooperative subunits

210 of the IFN- β enhanceosome expression of E6 blocks IFN- β gene activation upon viral infection
 211 (103). E6 binds to Tyk-2 and competes for Tyk-2 binding to the interferon receptor subunit
 212 IFNAR1. Thus, E6 inhibits the downstream activation of the Jak-STAT1-STAT2 pathway (65), and
 213 cells poorly respond to exogenous IFN treatment. Further downstream of this pathway, E7 binds
 214 to IRF9 and inhibits the transcriptional activity of the ISGF3 enhanceosome made of IRF9, STAT1
 215 and STAT2 (6, 7). Thus, altogether, E6 and E7 block both the activation of the type I IFN gene
 216 and the IFN activation of the innate antiviral immunity as shown by the severe down regulation of
 217 IFN-responsive genes (85). Last but not least, since apoptosis induced by IFN- α/β depends upon
 218 p53 (97), the E6-mediated degradation of p53 further contributes to prevent death of the virus
 219 infected cells.

220
 221

222 **3) Herpes simplex virus ICP0: a dual E3-Ubiquitin ligase**

223

224 Herpes simplex virus-infected cell protein 0 (ICP0, also called vmw110) was initially
 225 described as a protein found to accumulate in infected cells, but not present in the virion. It acts
 226 as a promiscuous transactivating signal, since expression by transfection results in the activation
 227 of numerous cellular genes (see (46) for review).

228

229 ***Gene and structure***

230

231 ICP0 is coded by $\alpha 0$ which is transcribed in several spliced mRNA subspecies. The 775
 232 aa long protein is extensively post-translationally processed and the pattern of isoform expression
 233 vary with the progress of the infection. It contains a nuclear localisation signal and a self-
 234 interacting domain leading to formation of dimers and higher ordered multimers.

235

236 ***E3 Ubiquitin ligase activity***

237

238 ICP0 dynamically interacts with the proteasome (121) and is the only known ubiquitin
 239 ligase protein exhibiting two independent E3 sites (47). ICP0 has a RING domain and a HUL-1
 240 domain close to its NH₂ and COOH terminus respectively (FIGURE 3).

241

242 The RING domain is responsible for the recruitment of both of the cellular E2 ubiquitin
 243 conjugating enzyme UbcH5a (13) and one cellular substrate, the ubiquitin-specific protease
 244 enzyme USP7 (also called HAUSP) (35).

245

246 ICP0 is its own substrate for ubiquitination (16). It also directly ubiquitinates USP7 in vitro
 247 and in vivo, and, this activity leads to a reduction in cellular USP7 levels during HSV-1 infection
 248 (35). Conversely, USP7 stabilizes ICP0 in vitro and in vivo by protecting ICP0 from auto-
 249 ubiquitination (16). These reciprocal activities of the two proteins mimic the USP7-mediated
 250 stability of Mdm2 (64). The outcome during productive HSV-1 infection is that the USP7-mediated
 251 stabilization of ICP0 is dominant over ICP0-induced degradation of USP7 (10).

252

253 The ICP0 mediated ubiquitination of p53 is weak compared to that of Mdm2, the major
 254 cellular E3 ubiquitin ligase which keeps the p53 in low level in uninfected cells. ICP0 binds to p53
 255 by residues 241 to 594 and then promotes low levels of p53 ubiquitination in infected cells (11).

256

257 Other cellular proteins targeted for proteasome-mediated degradation by the ICP0-
 258 UbcH5a complex are the catalytic subunit of DNA protein kinase (DNA-PK) (93), the centromeric
 259 proteins CENP-C and CENP-A (34, 77) and two major components of the nuclear substructure
 260 ND10, the promyelocytic leukemia antigen PML (12, 20) and small ubiquitin-like modifier
 261 (SUMO)-modified forms of SP100 (20, 92). In cells expressing ICP0, PML can be easily
 262 destroyed, but neither PML nor its SUMO-modified forms has been successfully ubiquitinated
 263 directly in vitro by ICP0 (12). Thus an additional factor or some unknown substrate may be
 264 required to form an active E3 ligase complex for in vivo degradation of PML and/or sp100. In cells
 265 expressing dominant-negative UbcH5a, but not dominant-negative UbcH6 or UbcH7, blocks ICP0
 RING-mediated PML and sp100 degradation and can delay ND10 disruption by at least several
 hours (43).

266

267 The second ubiquitin ligase domain HUL-1 within ICP0, is not a Zn-finger and is required
 268 for the ubiquitination of the E2 ubiquitin ligase UbcH3 (cdc34) (121). UbcH3 is the major E2

enzyme which forms a complex with skp1-skp2-F-box and promotes the degradation of cyclin D1 and cyclin D3 (see (25) for review). ICP0 was found to stabilize both cyclins D3 and D1, without evidence for a direct interaction with cyclin D1 (121). Ubch3 strongly interacts with ICP0 20-241 region, which encompasses the RING domain, and moderately to ICP0 621-625 or HUL-1 domain (47). Only the latter domain and aspartate 199 are essential for ubiquitination and degradation of Ubch3, since, in cells infected with HSV-1, ICP0 with disrupted RING domain has no effect on Ubch3 degradation. Thus, N-terminus of ICP0 would indirectly contribute to the ubiquitination of Ubch3 by capturing it and pushing it towards the second ligase activity site (46).

Cellular impact and counteraction of innate immunity

Owing its numerous substrates and multiple molecular partnerships, ICP0 interferes with many viral and cellular functions. ICP0 with intact RING finger stimulates lytic infection and reactivates quiescent HSV-1 viral genomes (see (46) for review). HSV-1 mutants devoid of ICP0 are less cytotoxic and less pathogenic. Disruption of kinetophore due to polyubiquitination of CENP subunits by ICP0 results in abnormal chromosome segregation, unusual cytokinesis, and nuclear morphological aberrations: cells become stalled at an unusual stage of mitosis defined as pseudoprometaphase (34, 54, 76). However, the impact of ICP0-mediated Ubch3 degradation and resulting cyclin D1 and D3 stabilization remains unclear in HSV infected cells (33).

ICP0 is clearly involved in the dampening of the (i) development of antiviral state and (ii) the amplification through the IFN \leftrightarrow IFNAR pathway.

(i) During infection by HSV-1, there is little expression of interferon stimulated genes (ISGs), whereas cells infected by mutant ICP0^{null} HSV-1 exhibit high level of ISG expression (32). A significant part of this ISG expression is likely independent from the elicited IFN response since it is insensitive to a protein synthesis inhibitor (82, 87, 99). ICP0 acts by inhibiting IRF-3-mediated activation of ISGs (69, 81). This inhibition critically relies on intact RING domain and active proteasome-dependent proteolysis (32, 69). IRF-3 turn-over is increased and nuclear accumulation of IRF-3 is blocked by ICP0 (81), but ICP0 does not induce the degradation of TBK1, IRF-3, IRF-7, or CBP which all belong to the IRF-3 signalling pathway (69).

(ii) While wild type HSC-1 is relatively insensitive to exogenous interferon α/β treatment of host cells, the growth of ICP0^{null} HSV-1 is inhibited in Vero cells pretreated by type I interferon (49, 83, 84). Moreover, mutant ICP0^{null} HSV-1 poorly replicates in mice, a phenotype which is reverted in IFNAR^{-/-} mice (63).

How does E3 ubiquitin ligase activity of ICP0 can contribute or even be responsible for the ICP0 blocks of the induction of an antiviral state ?

(1) The ICP0 mediates the degradation of PML which is required for the interferon response. Indeed, exogenous IFN does not induce an efficient antiviral state in PML^{-/-} cells and does not affect the growth of ICP0^{null} HSV-1 in these cells (19). Interestingly, CBP/p300, which are subunits of the enhanceosome downstream to the IRF-3 pathway, bind to PML (106) and their nuclear distribution is strongly modified in HSV-1 infected cells provided that ICP0 with an intact RING domains is expressed (69).

(2) DNA-PK stabilizes IRF-3 (60), and ICP0-mediated targeting of DNA-PK for degradation may contribute to the weakening the IRF-3 activation pathway.

(3) P53 is up-regulated by IFN to mediate apoptotic signal (97). ICP0 mediated targeting for degradation of p53 can contribute to the resistance of HSV to IFN.

In conclusion, ICP0 is an E3 Ubiquitin ligase which targets several cellular proteins, some of them being involved in the cellular innate immunity. We propose that the potent anti-innate immunity properties of ICP0 results from the coordinate disruption of several innate immunity pathways. Furthermore, at a late stage of HSV-1 infection, ICP0 prevents the degradation of rRNA according to a new antiviral mechanism distinct from the IFN-induced RNase L pathway. This effect, however, does not requires an intact RING domain (111).

4) Adenovirus E4orf6 and E1B55K protein: substrate recruiting sub-units of an E3 ligase

Human adenovirus has evolved strategies to regulate cellular proteins function to permit efficient viral replication. The viral E1B-55K/E4orf6 ubiquitin ligase is also required for efficient

322 viral late protein synthesis in many cell types, but the mechanism is not understood.
 323

324 **Genes and structures**

325 E4orf6 and E1B55K are two genes expressed early after adenovirus infection. They
 326 encoded a 34 kDa and 55 kDa proteins, respectively. E4orf6 belongs to the virus genes involved
 327 in the virus transcription and cell cycle control and E1B55K participates in inhibiting apoptosis.
 328

329 **E3 ligase activities**

330 In productively infected cells, adenovirus E4orf6 and E1B55K redirect the cellular E3
 331 ligase complex made of RING protein Rbx1/Roc1, Cullin 5, Elongin B and C (FIGURE 4) to target
 332 p53 for polyubiquitination and degradation (1, 18, 48, 100-102, 112) (see also (8, 105) for review).
 333 Infection with mutant viruses that do not express either E1B55K or E4orf6 proteins does not
 334 induces p53 degradation (112). E4orf6/E1B55K E3 ligase complex is remarkably similar to the
 335 Von Hippel-Lindau tumor suppressor and SCF (skp-Cul1) E3 ubiquitin ligase complex. Rbx1
 336 interacts with E4orf6 but not with E1B55K (100), and looks acting as a substrate specificity factor.
 337 This complex interacts with the E2-conjugating enzyme Ubch3 to conjugate ubiquitin chains to its
 338 substrates. E1B55K is the substrate recognition subunit of this complex. Both E4orf6 and
 339 E1B55K contain putative BC-box, but only E4orf6 directly interacts with Elongin C via its BC-Box
 340 motif. Furthermore, E1B55K also does not bind stably to isolated E4orf6 and requires E4orf6 to
 341 be in complex with Cul5 and Elongins B and C. The formation of the complex is thought to alter
 342 the conformation of E4orf6 and stabilize the interaction between E4orf6 and E1B55K (9). E4orf6
 343 and E1B 55K bind p53 near its N and C termini, respectively. The ligase complex activity is also
 344 critical dependent on NEDD8 which modifies the activity of Cullin5 (90, 100, 102). The E2
 345 conjugating enzyme Ubch3 (cdc34) is associated with E4orf6 in vivo, and, in an in vitro
 346 ubiquitination test, Ubch5 acts as a functional E2 enzyme (100).

347 E1B55K/E4orf6-Elongins B/C/Cullin5/Rbx1 E3 ligase complex can target one or more
 348 subunits of the MRN complex involved in DNA double-strand break repair for proteasome-
 349 mediated degradation (114), although there is no direct evidence for MRN single subunits to be
 350 polyubiquitinated. E1B55K/E4orf6/elonginBC/Cullin5/Rbx1 also exploits the cellular aggresome
 351 response to accelerate the degradation of MRN complexes in adenovirus-infected cells (74).
 352 Aggresome formation may contribute to protect the viral genomic DNA from MRN activity by both
 353 sequestering MRN in the cytoplasm and dramatically promoting its degradation by the
 354 proteasome.

355 During the late phase of infection by adenovirus, E1B55K/E4orf6 complex promotes the
 356 nuclear export of viral mRNA and prevents that of cellular mRNAs (see (8) for review). Does the
 357 E1B55K/E4orf6 E3 ligase complex also target a mRNP protein involved in most cellular mRNA
 358 nuclear export and enhances export and translation of late viral mRNA (8) ?

359 E4orf6 can interact with p53 and inhibit its transactivating activity (18, 28). In the absence
 360 of E4orf6, E1B55K dramatically increases the concentration of p53 (79). But p53 transactivating
 361 activity is blocked. Possibly, upon interaction with p53, E1B55K bring a repression domain close
 362 to the p53 activating domain (8). E1B5K also inhibits the acetylation of p53 by PCAF and thus
 363 contributes to p53 inhibition by another mechanism (73).
 364

365 **Cellular impact and counteraction of innate immunity**

366 Adenoviruses have developed several genes to control the antiviral effect of innate
 367 immunity (see (14) for review). Lowering the p53 contents of the cell by E4orf6 and E1B 55K
 368 proteins likely contributes to protect the infected cells from IFN induced p53-dependent apoptosis
 369 (97). Furthermore, by blocking nuclear export of cellular mRNA, they may have a major impact on
 370 the expression of IFN and ISG genes.
 371

372

373 **5) Lentivirus VIF protein: a substrate recruiting sub-unit of an E3 ligase**

374

375 The viral infectivity factor VIF encoded by HIV-1 and most other lentivirus was initially
 376 found in the nineties to be required for replication in "non permissive" cells such as primary T cells
 377 and macrophage but dispensable for replication in epithelial cell lines. More than ten years later,

378 the cellular target APOBEC3G was identified (see (104) for review).

379

380 **Gene and structure**

381 VIF is coded within the region on an alternative codon frame and has a size of about 23
382 kDa. Functionally, VIF shared many features with the adenoviral E4orf4 protein.

383

384 **E3 ligase activities**

385 VIF contains a BC-like-box (or SOCS-Box) (126, 128) to recruit Elongin C/B (FIGURE 5).
386 Binding to Elongin-C is negatively regulated by serine phosphorylation of the BC-box (80). VIF
387 does not have a Cul-Box, but contains a HCCH motif (Hx5Cx17-18Cx3-5H), with potency to
388 coordinate a zinc atom, the integrity of which is required for binding to Cullin 5 (78). In addition it
389 binds to the RING containing Rbx1 E3 ligase subunit (126). Vif connects the APOBEC3G and
390 APOBEC3F (apolipoprotein B mRNA-editing enzyme) as a substrate to the multisubunit E3 ligase
391 for polyubiquitination and degradation (71, 126). The active E2 ligase recruited by the RING
392 domain of Rbx1 has not been defined in vivo, although Ubc12 and Ubc5A can work in vitro. The
393 loss of function of VIF mutants correlates with their inability to bind to APOBEC3G or to give rise
394 to functional E3 ligase (61). VIF is also autoubiquitinated by the same E3 ligase complex which
395 explains its short half-life in vivo (40, 71, 80). Overexpression of APOBEC3G stabilizes Vif
396 expression as if the two substrates compete with each other (71). Thus, VIF functions like an F-
397 box protein by bringing together the Cul5 complex and the substrate.

398 Surprisingly, APOBEC3G is also monoubiquitinated by the unimolecular HECT-type E3
399 ligase Nedd4.1, for its efficient packaging within budding virions (30). Thus, APOBEC3G is the
400 substrate for both monoubiquitination and polyubiquitination by two separate E3 ligases.

401 Besides targeting APOBEC3G for ubiquitination and degradation, VIF may also directly
402 inhibit its deaminase activity, as suggested in experiments performed in *E. Coli* (108).

403

404 **Cellular impact and counteraction of innate immunity**

405 APOBEC3G is a cytidine deaminase which deaminates cytidine to uracil, resulting in
406 deleterious overmutagenesis of the HIV-1 genome. Furthermore, APOBEC3G displays another
407 anti-HIV-1 activity which is independent from its cytidine deaminase activity (86). Vif activity is a
408 species-specific factor because it cannot recognize APOBEC3G from other species which differ
409 by a single residue within the binding site (D128K) (71). This intrinsic cellular immunity belongs
410 also to the inducible innate immunity since a type I IFN treatment can upregulate the APOBEC3G
411 expression (118).

412

413

414 **6) Rubulavirus V proteins: a substrate recruiting sub-unit of an E3 ligase**

415

416 Rubulavirus are enveloped RNA viruses whose replication occurs entirely within the
417 cytosol. Their genome code for less than ten proteins, nevertheless because they also have to
418 cope with the cellular innate immunity, at least one of them, V protein, is a potent inhibitor of the
419 interferon system. As adenovirus EE4orf6 and Vif, V protein acts a scaffold linking a multi-subunit
420 cellular E3 ligase to new cellular substrates.

421

422 **Gene and structure**

423 Members of the *Rubulavirus* genus (simian virus 5 -SV5-, human parainfluenza virus 2 -
424 hPIV2- and mumps virus) which belongs to the *Paramyxoviridae* family and *Monogavirales* order
425 have a negative strand RNA whose genome contains 7 genes coding for 8 proteins. Indeed the
426 second gene codes the P protein, a polymerase cofactor, and, upon editing of P mRNA, to V
427 protein. V is two hundred amino acid long, shares a common N sequence with P and has a minor
428 C-terminus rich in Cys residues, a hallmark of all *Monogavirales* V protein. This C-terminus is a
429 new Zn-finger with no homology with other known Zn-finger structures (66).

430

431 **E3 ligase activities**

432 Rubulavirus V proteins were initially characterized for their ability to bind to the highly
433 conserved UV-damaged DNA-binding protein DDB1 protein (68) (FIGURE 6). DDB1 has a

434 multipropeller structure associating three β -propellers called BPA, BPB and BPC and one C-
 435 terminal helical domain (66). SV5 V binds to the BPA-BPC double propeller pocket by inserting its
 436 N-terminal helix, while the Zn-finger does not interact with DDB1. The BPC propeller DDB1 docks
 437 to the N-terminus of the E3 ligase Cul4A scaffold (66). Cul4A can recruit the Rbx1 RING protein
 438 (or another protein ?) which in turns recruits a yet to be defined E2 ligase. Mumps V protein binds
 439 also to this later protein (120). V proteins from SV5, mumps and hPIV2 multimerize and bind to
 440 STAT2. A single residue (Asn100 in V from SV5) located in a β -sheet determined efficient
 441 binding to STAT2 (66, 125). Only hPIV2 V can directly target STAT2 as an ubiquitination
 442 substrate, although V from SV5 can do so in vitro (98, 120). Instead, STAT2 is used by V proteins
 443 from SV5 and mumps as a scaffold to recruit STAT1 which is polyubiquitinated and degraded by
 444 the proteasome (3, 27, 119). Mumps V can also recruit directly STAT3 for ubiquitination and
 445 degradation, the later process for which the recruitment of Rbx/Roc1 is required (120)

446 447 **Cellular impact and counteraction of innate immunity**

448 STAT1-STAT2 heterodimers associated with IRF9 constitute the critical transactivating
 449 complex downstream the signalling induces by IFN binding to IFNAR. By downregulating STAT1,
 450 V protein is predicted to render mumps, SV5 and hPIV2 viruses less sensitive to IFN-mediated
 451 antiviral effect. Indeed, the inability of V protein to target mouse STAT1 correlated well with the
 452 very poor replication of SV5 in mice, whereas STAT1^{-/-} mice are sensitive to viral infection (see
 453 (51) and references herein).

454 However, in vitro, the phenotype of recombinant SV5 virus with C-truncated V protein is
 455 complicated, because V exhibits many other functions. (i) It binds to MDA5 (melanoma
 456 differentiation-associated gene 5), a companion molecule of the RIG-I-dependant IFN- β activation
 457 pathway (2, 51). (ii) V acts as an anti-apoptotic factor (115). Interestingly, all these functions
 458 require an intact Zn-finger. (iii) In a minigenome replication model, V protein exhibits transcription
 459 and replication inhibition properties (70).

460 The functional impact of STAT3 degradation by mumps V protein remains to be clarified
 461 since the role of STAT3 is variable according to the cell type (113).

462 463 464 **Conclusion**

466 We have illustrated, in this review, the various strategies used by viruses to hijack the
 467 ubiquitination pathway and target cellular proteins for degradation (or disrupting their function ?)
 468 in order to evade cellular innate antiviral response. Can a virus act also by inhibiting cellular
 469 ubiquitination ? The answer is probably yes, as revealed by the ability of measles virus P protein
 470 to inhibit ubiquitination and stabilize the RING-type E3 ligase PIRH2 protein (a homolog of
 471 MDM2), although the physiological relevance of this observation remains to be uncovered (22).
 472 This short survey has brought a glimpse of what we predict will be an increasing area of
 473 knowledge, namely the subversion or the use of ubiquitination and related peptide conjugation
 474 such as sumoylation and ISGylation by viruses to adapt their cell host for optimal replication and
 475 survival in the context of a whole organism and population. Indeed, there are numerous cellular
 476 E3 ligases, some of which are upregulated by type I IFN (88), and beside the dozen of cellular
 477 proteins so far identified as antiviral weapons, there are likely many other cellular proteins which
 478 can exhibit non specific or specific antiviral activities. For example, one of the gene is ISG15
 479 which is an ubiquitin-like protein, that, on one hand, targets the release of HIV-1 (91), and, on
 480 another hand, has its conjugation property inhibited by the Influenza B virus NS1 protein (129).

481
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483 **FIGURE legends**

484

485 **FIGURE 1.** Intrinsic catalytic E3 ligase activity of KSV RTA protein.

486

487 **FIGURE 2.** E6-AP independent (upper) and E6-AP dependent E3 ligase activity of HPV E6
488 protein, known substrates (dot lined), binding (full lined) partners and possible effect on innate
489 immunity. For symbols see FIGURE. 1.

490

491 **FIGURE 3.** Current view of E3 ligase activity of HSV ICP0 protein: known substrates and possible
492 effect(s) on cellular functions. The molecular support for the recruitment of sp100, PML, CENP-
493 A/C and DNA-PK as the substrates for ICP0 E3 ligase activity is yet unknown. For symbols see
494 also FIGURE. 1.

495

496 **FIGURE 4.** E3 ligase activity of adenovirus E4orf6 and E1B55K proteins. E1B55K is stably bound
497 to E4orf6 only when the latter is in complex with Cullin 5 and Elongins B/C. For symbols see
498 FIGURE. 1.

499

500 **FIGURE 5.** E3 ligase activity of HIV-1 Vif protein resulting in self and APOBEC-3G
501 polyubiquitination. Vif is also monoubiquitinated by HECT-type E3 ligase Nedd4-1 which results in
502 the efficient Vif encapsidation into virions. For symbols see FIGURE. 1.

503

504 **FIGURE 6.** E3 ligase activity of Rubulavirus V protein. Mumps V interacts directly with
505 Roc1/RBX1, and recruit STAT3 as ubiquitination substrate. Mumps and SVF5 interacts with
506 STAT2 solely to recruit STAT1 as the ubiquitination substrate. HIPV2-V protein binds and targets
507 STAT2 for ubiquitination. Roc1/RBX1 looks dispensable for STAT1 or STAT2 ubiquitination by
508 any V protein. For symbols see FIGURE. 1.

509

510

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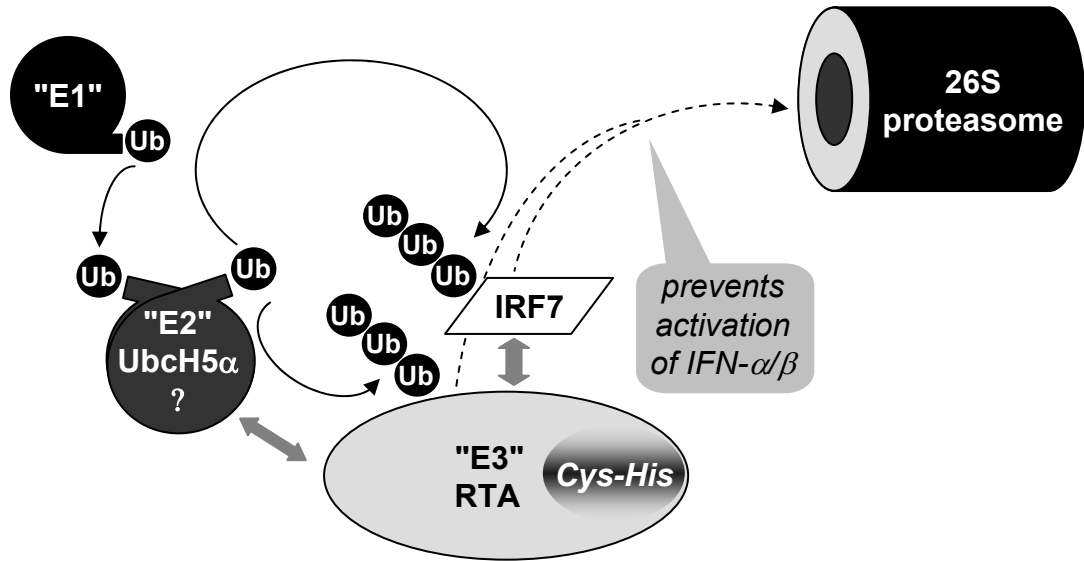
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symbols



Ubiquitination



degradation



interaction

