Review

Caspase cleavage of viral proteins, another way for viruses to make the best of apoptosis

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Viral infection constitutes an unwanted intrusion that needs to be eradicated by host cells. On one hand, one of the first protective barriers set up to prevent viral replication, spread or persistence involves the induction of apoptotic cell death that aims to limit the availability of the cellular components for viral amplification. On the other hand, while they completely depend on the host molecular machinery, viruses also need to evade the cellular responses that are meant to destroy them. The existence of numerous antiapoptotic products within the viral kingdom proves that apoptosis constitutes a major threat that should better be bypassed. Among the different strategies developed to deal with apoptosis, one is based on what viruses do best: backfiring the cell on itself. Several unrelated viruses have been described to take advantage of apoptosis induction by expressing proteins targeted by caspases, the key effectors of apoptotic cell death. Caspase cleavage of these proteins results in various consequences, from logical apoptosis inhibition to more surprising enhancement or attenuation of viral replication. The present review aims at discussing the characterization and relevance of this post-translational modification that adds a new complexity in the already intricate host-apoptosis-virus triangle.

Apoptosis Faces Up Viruses: Die Hard

When a viral infection threatens cells, one of the first measures they take is to induce apoptosis to restrict viral replication and spread.1–3 Dying this way, host cells are likely to generate specific signals aiming at triggering the immune system with innate and/or adaptative responses allowing the eradication of the invader.4,5 On the other hand, viruses have evolved a huge arsenal of strategies meant to either counter- or deal with this destructive process to ensure their survival.6–8 Apoptotic cell death is accompanied by characteristic morphological changes (cellular rounding-up and volume reduction, chromatin condensation, nuclear fragmentation, plasma membrane blebbing…) and at a molecular level by the activation of first initiator and then effector cysteinyl aspartate proteinases or caspases.9,10 Activated caspasases act through a catalytic Cys that hydrolyzes peptide bonds within the substrate, with a stringent specificity for Asp residue at P1 position (the nature of residues at positions P2, P3 and P4 depending on the caspase). Caspase substrates include a large number and variety of cellular proteins that participate through their cleavage to the strong apoptosis-related morphological changes, as well as other physiological processes. Interestingly, viral proteins are also likely to be cleaved by caspases but until 2004, only four of them were reported as such and suggested as advantaging the associated viruses through their cleavage.11 Since, their number has greatly increased and at least 16 viruses are now known to express proteins that undergo caspase cleavage. Here, we aim at updating these cleavages and discussing their biological relevance. From apoptosis inhibition to the improvement or attenuation of viral amplification, caspase cleavage of VPs highlights a potential new fascinating viral strategy to handle apoptosis induction.

Caspase Cleavage as a Way for Viruses to Counteract Apoptosis: Die Another Day

Apoptosis induction by infected cells is meant to jeopardize viral replication. Therefore, many viruses have developed strategies to inhibit this process through various mechanisms. Among them, inhibiting caspase activity through the cleavage of viral proteins constitutes an effective way to achieve apoptosis suppression (Table 1).

Baculoviruses are invertebrate viruses that encode several antiapoptotic products including IAPs, P49 and P35. When lacking P35, the baculovirus prototype Autographa californica multicapsid nucleopolyhedrovirus (AcMNPV) induces apoptosis and fails to replicate, whereas P35 rescue inhibits cell death and restores viral replication.12 Interestingly, P35 is proteolytically cleaved on infection13,14 and the 84DQMD87 cleavage site is required for P35-mediated apoptosis suppression. P35 directly inhibits many caspases, including...
Table 1: Characteristics of caspase cleavages of viral proteins leading to apoptosis inhibition

| Caspase-related products and suggested functions | References |
|-----------------------------------------------|------------|
| Caspase(s) induced on infection               |            |
| Cleaved proteins                             |            |
| Caspase cleavage site(s)                      |            |
| In vitro broad range of effector caspases from |            |
| both initiator and effector caspase           |            |
| Double-stranded DNA                          |            |
| Caspase(s) able to cleave in vitro or in cellulo | 13,15,17   |
| Two products of 15 and 20 kDa that remains stably associated with the caspase cleavage site(s) | 18,19      |
| Acts as a dimer through a covalent thioester bond | 16,17      |
| Comparables to P35, P49, and AAP-1            | 20,21,52   |
| Caspase cleavage of viral proteins were recapitulated in tables according to the functional consequences on viral life cycle they were shown or suggested to exert. The name of the virus, nature of its genome and caspase(s) induced on infection are indicated. The characteristics of the cleavages were also summarized, with identity of the cleavage site(s), caspase(s) able to cleave in vitro or in cellulo (sometimes different from caspases induced in cells undergoing infection) and suggested functions of the caspase-related products as often as possible. Vertical black arrows indicate where cleavage occurs.

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For baculoviruses and WSSV, inhibiting apoptosis is crucial to achieve their life cycle. These different invertebrate-infecting viruses encode proteins exhibiting active caspase cleavage sites, just as cellular substrates do, but with the special ability to irreversibly freeze the protease activity. This leads to a very potent and broad caspase inhibition, which keeps the host cell machinery available and fit for viral amplification.

Caspase Cleavage as a Way for Viruses to Replicate and Spread: Live and Let Die

Unlike the expression of antiapoptotic products, the requirement of apoptosis for viruses to survive is a way more counterintuitive strategy that yet has been evolved by several viruses and involves caspase cleavage (Table 2).

Parvovirus Aleutian mink disease virus (AMDV) can lead, at a single cell level, to either permissive infection, namely high levels of both viral DNA replication and production of viruses, or persistent infection with low viral DNA replication and almost no production of progeny virions. On permissive infection, AMDV induces caspase activation that is necessary for viral amplification. This requirement was associated with NS1 protein being cleaved through two caspase 3 sites leading to five NS1-related products. When one site is mutated within AMDV molecular clones, the viral production is strongly reduced and even aborted when both sites are disrupted. Interestingly, wild-type (WT) NS1 protein, which exerts replicative and transcriptional functions, is mostly nuclear, but when one of its cleavage sites is disrupted, the protein remains cytosolic resulting in a dramatic decrease in NS1-dependent viral protein (VP) expression. NS1-related C-terminal products, also nuclear, are suggested to be actively
Table 2. Characteristics of caspase cleavages of viral proteins favoring viral replication and spread

| Virus         | Genome type                  | Caspase(s) induced on infection | Cleaved proteins | Caspase(s) able to cleave | Caspase cleavage site(s) | Cleaved protein(s) | Caspase-related products and suggested functions |
|---------------|------------------------------|--------------------------------|------------------|--------------------------|--------------------------|---------------------|--------------------------------------------------|
| AMDV          | Single-stranded DNA          | Caspases 3 and 7                | NS1              | Caspases 3, 6, 7, 9      | 224INTD227 k            | 282DQTD285 k        | Two N-terminal stable products, two C-terminal stable products, that might facilitate nuclear translocation of full-length NS1, required for the generation of VP70, yielding fully infectious viruses. |
| HPV           | Double-stranded DNA          | Caspases 3 and 7                | E1               | Caspases 3, 8 and 9      | 46DMVD49 k              | 25                  | 'cleaved E1' in vitro: caspases 3, (4), 8 and 9 in cellulo (sometimes different from caspases induced in cells undergoing infection) and suggested cleavage site leaves uncertainty regarding the D residue actually targeted. |
| SARS-CoV      | Single-stranded positive RNA  | Caspases 3, 5, 6, 7, 8, and 9   | VP90             | Caspases 3, (4), 8, and 9 | 654TYVD657 k            | One stable product referred as 'proteolytic cleavage product' caspases 3 and 6 (pharmalogical inhibitors). |

Caspase cleavages of viral proteins were recapitulated in tables according to the functional consequences on viral life cycle they were shown or suggested to exert. The name of the virus, nature of its genome and caspase(s) induced on infection are indicated. The characteristics of the cleavages were also summarized, with identity of the cleavage site(s), caspase(s) able to cleave and/or in cellulo (sometimes different from caspases induced in cells undergoing infection) and suggested cleavage site leaves uncertainty regarding the D residue actually targeted. Interestingly, both intracellular VP90 processing into VP70 and progeny virion release are lost in the presence of a pan caspase inhibitor. However, in opposition to what was first suggested, viral release needs caspase activation but does not need VP90 processing into VP70 to be achieved.27

But yielding fully infectious viruses does require shorter polypeptides to be created through VP70 further processing by trypsin. Thus, first cleaving VP90 to generate VP70 likely represents a crucial intermediate event during HAstV infection.

SARS-coronavirus (SARS-CoV) is a fairly new RNA virus responsible for a severe acute respiratory disease. SARS-CoV leads to either permissive or persistent infection, with strong cytopathic effects and high viral titers or the opposite, respectively. Interestingly, the nucleocapsid protein (N), that has both structural and non-structural functions, is proteolytically processed in cells undergoing a lytic cycle or ectopically expressing the viral genome.29 Using a pharmacological approach, N protein was demonstrated to be targeted by caspases 3 and 6. On permissive infection, N protein localizes in both cytosol and nucleus while remaining cytosolic in cells undergoing persistent infection. Moreover, preventing N from translocating to the nucleus by mutating its nuclear localization signal abolishes its cleavage by caspases. Thus, permissive infection is associated with N being translocated to the nucleus and possibly its ensuing caspase cleavage. Nevertheless, the mechanisms underlying viral replication, N subcellular localization and N caspase processing are unknown so far.

In sharp contrast with baculoviruses and WSSV, several very different viruses evolved to hijack apoptosis with caspase cleavage being required to reach optimal viral amplification. Based on the well-described case of AMDV, we can

involved in the transport of WT NS1. Therefore, on apoptosis induction, full replication occurs, leading to permissive infection. Conversely, without caspase activation, AMDV amplification would be limited and that might allow this lytic virus to establish persistent infection.

Human papillomavirus (HPV) is mostly known to infect epithelial cells of the genital tract and cause cervical cancers. On epithelial differentiation, HPV induces a DNA damage response that leads to caspase 3-dependent apoptosis.24 Interestingly, HPV E1, a protein involved in viral DNA replication, is a target for caspases 3 and 7 at a site that is conserved in all genital HPVs and preventing E1 cleavage reduces viral amplification. When compared with chemically induced apoptosis, HPV-induced apoptotic markers are limited. Interestingly, HPV increases the levels of both antiapoptotic Bcl2 and Survivin proteins.25 HPV pro- and antiapoptotic properties might achieve a caspase activity threshold that is sufficient for E1 cleavage and viral amplification, but not lethal for the host cell. Besides E1, HPV E6 protein is cleaved by caspases as well, but the functional consequences remain unknown.26

Human astroviruses (HAstV) are responsible for gastroenteritis. In Yuc8 strain, orf2 encodes the precursor of viral capsid proteins, VP90, whose processing yields VP70. Besides, HAstV activates caspases 3, 4, 6, 7, 8 and 9.27,28 In vitro, caspases 3, 8 and 9 are able to target VP9027 but only caspase 3 or 9 silencing reduces VP70 generation on infection. Interestingly, HPV E1, a protein involved in viral DNA replication, is a target for caspases 3 and 7 at a site that is conserved in all genital HPVs and preventing E1 cleavage reduces viral amplification. When compared with chemically induced apoptosis, HPV-induced apoptotic markers are limited. Interestingly, HPV increases the levels of both antiapoptotic Bcl2 and Survivin proteins.25 HPV pro- and antiapoptotic properties might achieve a caspase activity threshold that is sufficient for E1 cleavage and viral amplification, but not lethal for the host cell. Besides E1, HPV E6 protein is cleaved by caspases as well, but the functional consequences remain unknown.26

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hypothesize that the caspase-related products created through cleavages display novel properties required for the achievement of the viral life cycle.

Caspase Cleavage as a Way for Viruses to Downregulate Their Own Expression: You Only Live Twice

In some cases, apoptosis induction by the host cell leads to exactly what is expected, namely viral attenuation, but surprisingly with the help of viral protein cleavages. The possible viral advantage resulting from such an event is discussed (Table 3).

*Kaposi sarcoma-associated herpesvirus* (KSHV) establishes long-term infections leading to Kaposi sarcomas and can go through either latent or lytic cycle. When KSHV is reactivated, ORF57 (or Mta or KS-SM) is detected by western blot as a doublet, with the smaller product being abolished by a pan caspase inhibitor. *In vitro*, caspase 7, which is activated on KSHV reactivation, and to a lesser extent caspases 5 and 10, are able to process ORF57 at 30DETD33. Interestingly, coexpression assays show that ORF57 cleavage product (i.e. ORF57 lacking residues 1–33) is no longer able to promote viral lytic gene expression. Accordingly, complementing a stable cell line containing an orf57-null KSHV genome with ectopic WT or uncleavable ORF57 promotes lytic gene expression, while ORF57 lacking residues 1–33 does not. Consistently, the number of cell-free virus particles dramatically increases when caspase 7 is inhibited. Thus, ORF57 cleavage would prevent proper expression of its downstream targets and subsequent full reactivation of KSHV, suggesting that it allows KSHV to maintain a persistent infection.

As described above, AMDV NS1 protein is cleaved by caspses, which allows full viral replication. Interestingly, AMDV capsid proteins VP1 and 2 are also processed by caspases on viral infection or ectopic expression. The cleavage generates a stable 26-kDa product, VPx, and can be partly prevented by the pharmacological inhibition of caspases 6, 8, 9 and 10, and completely by a pan caspase inhibitor. Besides, VP protein expression in either transfected or AMDV-infected cells mainly activates caspase 10, followed by caspases 6, 9, 3 and 7, with caspase 7 as the more efficient in VP cleavage *in vitro*. Altogether, these data argue for the involvement of several caspases in VP cleavage. AMDV-G strain grows more efficiently at 31.8°C than 37°C. The alteration of the caspase site within AMDV-G increases both virus particle dramatically increases when caspase 7 is inhibited. Thus, ORF57 cleavage would prevent proper expression of its downstream targets and subsequent full reactivation of KSHV, suggesting that it allows KSHV to maintain a persistent infection.

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transformed cells, mainly in a non-apoptotic manner. However H-1PV is able to activate caspases in non-transformed cells, leading to the cleavage of NS1, a non-structural protein (NS) notably involved in viral DNA replication and gene expression by transactivating P38 promoter, which controls the synthesis of capsid proteins. Cleaved NS1 protein (named NS1-Nterm) lacks its C-terminal transactivation domain. When ectopically expressed, NS1-Nterm acts as a dominant negative on NS1-driven P38 promoter transactivation, and dramatically decreases viral production. Moreover, a molecular clone expressing an uncleavable version of NS1 tends to generate more virions. As cancer cells are often refractory to proper apoptotic induction, we propose that H-1PV oncotropism is due, at least in part, to the inability of cancer cells to cleave NS1 protein, thus allowing strong virus production. On the other hand, NS1 cleavage would act as a sensor of antiviral defenses and accordingly attenuate viral amplification, likely to favor persistent infection (our unpublished results).

Crimean-Congo hemorrhagic fever virus (CCHFV) causes severe coagulation dysfunction in humans. CCHFV nucleocapsid protein (NP) is an important structural protein also involved in viral replication and, when ectopically expressed with an apoptotic factor such as Bax protein, it generates two fragments through cleavage at a consensual DEVD motif. A caspase 3 inhibitor and cells lacking caspase 3 both allows a one log-increase in the production of virions, which suggests that caspase activation is involved in CCHFV attenuation. Thus, NP caspase cleavage and/or NP-related products may participate to this attenuation although the mechanisms remain to be investigated. Interestingly, the caspase cleavage site is conserved within all the strains that were checked, suggesting that it is an important feature for CCHFV regulation.

Caspase cleavages of viral proteins can result in the attenuation of the virus. Rather than a weakness of the virus, this might be considered as a way for the virus to adapt to the cellular context: as a result of such viral attenuation, the host response is largely reduced while the virus keeps its ability to replicate to some extent.

Unknown Functions of viral protein Caspase Cleavages: On her Majesty’s Secret Service

Although the consequences of several caspase protein cleavages have been elucidated, they remain elusive so far for others (Table 4).

Influenza viruses are structured into ribonucleoprotein segments consisting of viral RNA and viral proteins, the major one being the NP. Unlike avian NP, NP proteins from human influenza A and B viruses are long known to be caspase targets. Human influenza with uncleavable (‘avian-like’) NP is dramatically less lethal for mice, along with lower viral titers and faster clearance than its WT counterpart. This argues for the involvement of NP caspase cleavage in the virulence of influenza virus. But making avian NP cleavable (i.e. making the protein ‘human-like’ by introducing the same caspase cleavage site) does not enhance the viral virulence as could have been expected. Thus, modulating influenza pathogenicity through NP caspase cleavage would be a specificity of human strains that cannot be extrapolated to avian ones. However, avian influenza pathogenicity might still be regulated by caspase cleavage. The viral ionic channel protein M2 protein is also cleaved by caspases, likely caspase 2 and/or 3 in both human and avian influenza viruses and was shown to be associated with avian influenza pathogenicity. Altogether, these studies highlight that modulating influenza caspase sites attenuates the virus although through currently unknown mechanisms.

Hepatitis C virus (HCV) often leads to chronic infection evolving to cirrhosis and possibly hepatocellular carcinoma. HCV core protein induces activation of caspases 2 and 6, and interacts with viral NS5A protein that is cleaved by the activated caspases. Several studies point to a role of NS5A caspase cleavage in its subcellular localization. The protein is mainly found in the cytosol while exerting nuclear functions. NS5A caspase cleavage was first suggested to allow the removal of a C-terminal cytoplasmic retention signal along with the translocation of the C-terminal deleted NS5A to the nucleus, reminding what was already described for AMDV NS1 protein. However, a study more recently reported a cytosolic localization of these C-terminal truncated forms of NS5A and no obvious role of NS5A caspase cleavage in its trafficking. Although its characterization is well admitted, the functional relevance of NS5A cleavage is still debated.

Transmissible gastroenteritis coronavirus (TGEV) causes acute and fatal diarrhea in newborn piglets. TGEV infection is able to induce caspases 3, 6, 7, 8 and 9activation and the cleavage of the structural NP N, leading to a stable 41-kDa fragment (N). N protein is targeted in vitro by caspases 6 and 7, and less efficiently by caspase 3. In HRT18jap1 cells, the infection causes apoptosis but is not productive, suggesting that caspase activation (and possibly N caspase cleavage) prevents progeny virion generation. However, caspase inhibition in this context does not restore any viral production. Owing to the lack of satisfactory tools, human HRT18jap1 cells were used as a study model but might not be appropriate to reveal N caspase cleavage relevance, notably for virus production. Further digging will thus be needed to understand the biological significance of N processing by caspases on TGEV infection.

Feline calicivirus (FCV) causes upper respiratory tract disease in cats. FCV capsid protein is synthesized as a precursor further cleaved by the viral protease. However, a 40-kDa product (P40) is also usually observed at late stages of FCV infection and can be abolished with a pan caspase or a caspase 3/7 inhibitor. Accordingly, FCV-infected cells undergo apoptosis as well as caspases 2, 3 and 7 activation. Only caspase 2 and far less efficiently caspase 6 process FCV capsid protein in vitro at cleavage sites that have not been described yet. As suggested for instance for AMDV, cleavage of the capsid protein might impair particle assembly and participate to viral persistence but this has not been investigated either.

Adenoviruses gather more than a 100 species with about 40 being able to infect humans. Adenovirus early region 1A (AdE1A) encodes two major proteins, 12S and 13S, that are involved in the control of early viral gene expression through their interactions with the host cell machinery. In vitro, caspases 3 and 7 are able to cleave both 12S and 13S proteins, although the cleavage efficiency depends on the
### Table 4. Characteristics of caspase cleavages of viral proteins with unknown functions

| Virus       | Genome type          | Caspase(s) induced on infection | Cleaved proteins | Caspase cleavage site(s)                                                                 | Caspase(s) able to cleave | Caspase-related products and suggested functions | References |
|-------------|----------------------|---------------------------------|------------------|------------------------------------------------------------------------------------------|---------------------------|--------------------------------------------------|------------|
| Influenza   | Single-stranded      | Caspase 3                        | Nucleocapsid protein | NP (in human strains) 13METD16 (predicted) 1579EEYD1586 (predicted) 20DVVD52 (predicted) | Prediction: caspases 6 and 8 | NP53 or aNP (53 kDa) aM2 (13 kDa)                | 34, 37, 38 |
|             | negative RNA         |                                 | M2 (in human and animal strains) | 257DSSD25 (predicted) | Prediction: caspases 2, 6 and 7 | Two stable products of 31 and 48 kDa in Satoh et al., 42 (genotype 1b) Two stable products of 17 and 31 kDa in Kalamvoki et al., 40 (genotype 1a) Putative functions still debated, with possible involvement in nuclear localization | 39, 40, 42 |
|             |                      |                                 |                  |                                                          |                            |                                                  |            |
| HCV         | Single-stranded      | Caspases 3 and 7 found activated in the hepatocytes of HCV-infected patients | NS5A            | 151XXXD154 (genotypes 1a and 1b) 286XXXD289 (genotype 1b) 348DXXD351 (found in almost all genotypes and strains) | In vitro: caspase 6 | Two stable products of 31 and 48 kDa in Satoh et al., 42 (genotype 1b) Two stable products of 17 and 31 kDa in Kalamvoki et al., 40 (genotype 1a) Putative functions still debated, with possible involvement in nuclear localization | 43, 44     |
|             | positive RNA         |                                 |                  |                                                          |                            |                                                  |            |
| TGEV        | Single-stranded      | Caspases 3, 6, 7, 8 and 9        | Nucleocapsid protein | 3056VVPD309 (predicted) | In vitro: caspases (3), 6 and 7 | One stable product referred as N’ (41 kDa) | 45, 46     |
|             | positive RNA         |                                 |                  |                                                          |                            | one stable product referred as p40 (40 kDa)     |            |
| FCV         | Single-stranded      | Caspases 2, 3 and 7              | Capsid protein    | 11 putative sites Cleavage at 228DTAD231 would be consistent with the generation of p40 | In vitro: caspases 2 and 6 | In cellulo: caspases 3/7 (pharmacological inhibitor) | 47         |
|             | positive RNA         |                                 |                  |                                                          |                            |                                                  |            |
| Adenoviruses| Double-stranded DNA  | Apoptosis induced on infection only with a TNFα treatment | AdE1A 12S and 13S | Depends on the serotype. Multiple cleavage sites supposed to occur in Ad12 with only one of the putative sites conserved in Ad5 | In vitro: caspases 3, 6 and 7 | Depends on the serotype | 48         |
| MCV         | Double-stranded DNA  | Lack of models for recapitulating the infection | MC160P            | 194LEVD197 (predicted) | In vitro: caspases 3 and 8 | Several stable products from 21 to 35 kDa |            |
| HSV-1       | Double-stranded DNA  | Apoptosis induction with d120 mutant | ICP22 or M(r) 37,500 | Not defined | In vitro: caspase 3 | One stable product named M(r) 35,000 |            |

Caspase cleavages of viral proteins were recapitulated in tables according to the functional consequences on viral life cycle they were shown or suggested to exert. The name of the virus, nature of its genome and caspase(s) induced on infection are indicated. The characteristics of the cleavages were also summarized, with identity of the cleavage site(s), caspase(s) able to cleave in vitro and/or in cellulo (sometimes different from caspases induced in cells undergoing infection) and suggested functions of the caspase-related products as often as possible. Vertical black arrows indicate where cleavage occurs.
Viruses Face Up to Apoptosis: Die Harder. There are clear evidences concerning the relevance of viral protein caspase cleavages in the physiology of viruses (Figure 1). Coherently, such a modification is used to directly fight apoptosis and AcMNPV as well as WSSV express proteins acting as strong and broad inhibitor caspase substrates. For other viruses, caspase cleavage probably allows the removal of specific regions that reveals or eliminates functional domains or signals. In some cases, this leads to full viral amplification (AMDV NS1, HPV E1), with the striking example of AMDV NS1 protein that needs to be cleaved by caspases to translocate to the nucleus and eventually exert its functions. On the contrary, caspase cleavage can result in the attenuation of the virus by generating new viral products acting as dominant negatives of NS proteins (H-1PV NS1, KSHV ORF57) or unfit for virus packaging when structural proteins are concerned (AMDV VP and possibly FCV capsid protein). Interestingly, such attenuation at a cellular level might hold importance regarding the possibility for viruses to establish permissive and/or persistent infection at a higher scale (i.e. multicellular organisms). The functional consequences of some viral protein caspase cleavages still remain debated or elusive because of the difficulty of investigating hazardous entities (influenza, HCV), the multitude of strains and genotypes (influenza, HCV, adenovirus) or the lack of appropriate tools such as cellular or animal models allowing to recapitulate the viral life cycle (TGEV, MCV). When caspase cleavages of viral proteins work in too mysterious ways, it is sometimes concluded that they constitute a mechanism of degradation resulting from the host fighting back the infection. However, the caspase-related products detected are mostly stable, suggesting they could be somehow involved in the viral life cycle as mentioned right above. Besides, knowing how high the mutation rates of viruses can be, or that some viral oncoproteins (like v-Rel) adapted to resist caspase cleavage through evolution unlike their cellular counterparts, keeping caspase cleavage sites seems very unlikely if viruses do not somehow profit from them. As caspase cleavage of viral proteins occurs in all sorts of proteins (structural or non-structural) and in all sorts of viruses (DNA as well as RNA), this suggests that it constitutes a strong strategy to handle apoptosis. By managing to use the molecular effectors of apoptosis to protect themselves from eradication without any additional genetic information required, viruses prove once again how fascinating their adaptability can be.
Conflict of Interest
The authors declare no conflict of interest.

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