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The Herpes Simplex Virus Type 1 Multiple Function Protein ICP27*

Lei ZHAO#, Wen-bo ZHU#, Qiong DING, Gui-qing PENG and Chun-fu ZHENG**

(State Key Laboratory of Virology, Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan 430071, China)

Abstract: The herpes simplex virus type 1 (HSV-1) infected-cell protein 27 (ICP27) is an essential, highly conserved protein involved in various steps of HSV-1 gene regulation as well as in the shut-off of host gene expression during infection. It functions primarily at the post-transcriptional level in inhibiting precursor mRNA splicing and in promoting nuclear export of viral transcripts. Recently, many novel functions performed by the HSV-1 ICP27 protein were shown, including leptomycin B resistance, inhibition of the type Ⅰ interferon signaling, regulation of the viral mRNA translation and determining the composition of HSV-1 virions.

Key words: Herpes simplex virus type 1 (HSV-1); Infected-cell protein 27（ICP27）; Nuclear export; Leptomycin B (LMB); Interferon (IFN)

Human herpes simplex virus type 1 (HSV-1), a nuclear replicating DNA virus, is a widespread human pathogen that causes a lytic infection in the mucosal epithelial cells and a life-long latent infection in neurons. During lytic infection, over 80 gene products are expressed in a highly regulated temporal cascade and can be divided into three classes: immediate-early (IE), early and late (18). HSV-1 infected-cell protein 27 (ICP27) is a 63 kDa immediate-early regulatory phosphoprotein homologous to gene products identified in all classes of herpesviruses so far, including Epstein-Barr virus (EBV) transactivator protein Mta encoded by BMLF1, ORF57 of Kaposi's sarcoma-associated herpesvirus (KSHV), ORF57 of Herpesvirus saimiri (HVS), ORF4 of Varicella-Zoster virus and UL69 in human cytomegalovirus (48).

HSV-1 ICP27 is an essential and multifunctional regulator of gene expression that modulates the synthesis and maturation of viral and cellular mRNAs (9). ICP27 inhibits pre-mRNA splicing (15, 40), stimulates pre-mRNA 3' processing (25), affects mRNA stability (2), and shuttles between the nucleus and the cytoplasm (33, 37, 45), promoting viral RNA nuclear export (3, 19, 37). In a study where use of deletions shows that ICP27 may contribute to HSV-1 leptomycin B (LMB) sensitivity (22). Much recent work in several laboratories has demonstrated that ICP27 has a role in promoting translation of viral mRNA (9, 10, 21). ICP27 is also involved in the inhibition of type I

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# Equal contribution author.

** Corresponding author.
Tel: +86-27-87198676, E-mail: zhengcf@wh.iov.cn

interferon (IFN) signaling (18, 25) and determining the composition of HSV-1 virions (41).

ICP27 SHUTTLES AND EXPORTS HSV-1 mRNAs

ICP27 is an RNA binding protein that shuttles between the nucleus and the cytoplasm (27, 28, 33, 37, 45). ICP27 contains an arginine and glycine-rich motif, the RGG-box, which allows it to bind to RNA (27). ICP27 also contains two nuclear localization sequences (NLS) (26) and a leucine-rich sequence that bears a strong resemblance to the nuclear export sequence (NES) of the human immunodeficiency virus (HIV) protein Rev (37). Rev mediates the export of HIV-1 mRNA by binding the cellular nuclear transport receptor chromosome region maintenance 1 (CRM1) through its NES, an interaction that is inhibited by LMB, an inhibitor of CRM1 (42). It has been demonstrated that the CRM1 plays a role in ICP27 export (24, 37). CRM1 recognizes its cargo proteins by binding directly to leucine-rich NESs in those polypeptides. However, Lengyel *et al.* have shown that ICP27 can efficiently exit the nucleus in the presence of LMB, suggesting that CRM1 does not mediate the nuclear export of ICP27 (22). Moreover, Koffa *et al*. reported that CRM1 is not required for ICP27-induced mRNA export in *Xenopus laevis* oocytes (19), and Chen *et al*. provided evidence that the leucine-rich NES of ICP27 does not require CRM1 for its activity (4).

Most of the recent evidence suggests that ICP27 utilizes the TAP (a non-karyopherin export receptor that mediates transport of mRNAs to the cytoplasm) system, believed to be the major pathway for bulk export of spliced cellular mRNAs (3, 8). It has been demonstrated that at later times, beginning at about 6 h after infection, ICP27 begins to shuttle between the nucleus and cytoplasm (4, 28, 33, 37, 45). ICP27 binds to HSV-1 mRNAs (27, 37, 44) and facilitates their export to the cytoplasm by interacting with the cellular RNA export adaptor protein Aly/REF (RNA and export factor binding proteins) and the cellular export receptor TAP/NXF (3, 4, 19, 27, 45). Aly/REF interacts directly with TAP/NXF1 (46), and excess Aly/REF increased the rate and efficiency of mRNA export *in vivo* (35). ICP27 binds to the cellular mRNA export factors REF and TAP in an RNase sensitive manner suggesting that RNA may be a stabilizing component of the ICP27 viral mRNA export complex (16). A similar observation has also been reported for EB2 and HVS ORF57 (16, 50).

It may be that the interactions of ICP27 with Aly/REF and TAP facilitate the export of viral mRNAs during wild-type infection, since ICP27 stimulates the export of viral intronless mRNAs, but not cellular mRNAs, after microinjection into *X. laevis* oocytes, although these interactions are not required for late mRNAs to be exported, the interaction of ICP27 with TAP/NXF1 occurs after ICP27 leaves viral transcription sites (19). However, Chen *et al.* reported that ICP27 interacts directly with TAP/NXF1 and does not require Aly/REF to bridge the interaction (3).

An earlier study shows that, ICP27 was required for efficient nuclear export of viral mRNAs (37). However, more recent studies have shown that ICP27 is not required in HSV-infected cells for efficient cytoplasmic accumulation of at least certain HSV-1 mRNAs (10), such as HSV-1 late mRNAs VP16, ICP5, gB, gC, and gD are all exported into the cytoplasm in the absence of ICP27 (9, 10). It is possible that viral late mRNAs are exported via a

different pathway in the absence of ICP27 or that viral late mRNAs continue to be exported via the REF/TAP pathway even in the absence of ICP27. Meanwhile, it has been reported that, TAP plays a role in promoting the translation of unspliced mRNAs (17), and Aly/REF enhances transcriptional promoter activity (47). It may be that the interaction of ICP27 with Aly/REF and TAP facilitates late mRNAs transcription and translation, respectively, and that the role in late mRNAs export is minimal (10).

ICP27 has been demonstrated to interact with RNA polymerase II (RNAPII) and facilitates its recruitment to viral transcription sites (6, 53), but it is not known whether, once RNAPII is localized to the viral transcription sites, ICP27-binding to RNAPII is required for ICP27-mediated viral mRNA export. Although the exact molecular mechanisms are still not clearly understood, exploring the mechanism of how the herpes viral mRNA export to the cytoplasm may advance the knowledge of the pathogenesis of the herpes viruses and may enable the development of new antiviral approaches (48).

ICP27 MEDIATES THE LMB RESISTANCE

It was previously shown that HSV-1 infection is sensitive to LMB (51). Because LMB has no known targets other than CRM1, it is presumed that the LMB sensitivity of HSV-1 infection reflects a need by the virus to utilize CRM1 during its lytic infection. However, Lengyel *et al*. reported that the amino N-terminus of ICP27 is involved in the LMB resistance, and an unexpected linkage between LMB resistance and the nucleocytoplasmic distribution of two other HSV-1 IE regulatory proteins, ICP0 and ICP4. The same amino (N)-terminal region of ICP27 that determines sensitivity to LMB also enhances ICP27's previously documented ability to promote the cytoplasmic accumulation of ICP4 and ICP0. Therefore they speculate that ICP27's effects on ICP4 and ICP0 may contribute to HSV-1 LMB sensitivity (22).

ICP27 INHIBITS TYPE Ⅰ IFN SIGNALING

Recent studies have shown that HSV-1 ICP27 is involved in the innate immune response (18, 29). ICP27 has been identified as an important viral protein counteracting the early innate immune response (29).

Because the innate immune response promotes viral clearance, it is important for HSV-1 to have processes that inhibit these pathways in order to productively infect the epithelial cells, establish latent infection, and persist in neurons throughout the life of the host (18). Several viruses have evolved strategies to evade type I IFN signaling at different stages of the pathway (20, 32, 52). Herpes viruses also have evolved anti-IFN signaling activities (18). HSV-1 has several mechanisms to inhibit type I IFN production, the activities of IFN-stimulated genes (ISGs), and the IFN signaling pathway itself (18).

Type I IFN (IFN-α/β) signaling is an important antiviral response that results in the expression of antiviral, antiproliferative, and immunomodulatory proteins (34). IFN-α/β binds the type I IFN receptor subunits (IFNAR-1 and -2), causing heterodimerization and phosphorylation of the subunits. This activation leads to the phosphorylation of the Janus kinases, Jak-1 and Tyk-2, which in turn phosphorylate signal transducers and activators of transcription (STATs) 1 and 2. The STATs heterodimerize and translocate into the nucleus, where they associate with p48 (also known as IRF-9), bind a *cis*-acting DNA

element called the IFN stimulated response element, or ISRE (34) for the transactivation of ISGs (12, 36).

In a study, Johnson *et al*. reported that the inhibition of the Jak/STAT pathway by HSV-1 requires viral gene expression and that viral immediate-early protein ICP27 plays a role in downregulating STAT-1 phosphorylation and in preventing the accumulation of STAT-1 in the nucleus (18). The reduced STAT-1 phosphorylation response to IFN-α treatment in cells infected with the ICP0 mutant could indicate that ICP0 is also involved in the inhibition of the Jak/STAT pathway. ICP0 has been shown to have many activities to counteract various stages of IFN signaling (14, 30, 31, 43), but because ICP27 expression is sufficient to inhibit IFN-α-induced nuclear accumulation of STAT-1, it seems that any role ICP0 might play in this process is secondary to that of ICP27 (18).

ICP27 REGULATES TRANSLATION OF VIRAL mRNAs

HSV-1 ICP27 protein is an essential regulator of viral gene expression with roles at various levels of RNA metabolism in the nucleus. More recently, intensive studies have shown that ICP27 can interact with host translation factors (10, 21) and enhance the translation of certain viral mRNAs (9, 10). The ICP27 C terminus is required for stimulation of translation (21).

The widely used tethered function assay of *Xenopus* oocytes was employed to test the effect of ICP27 on translation *in vivo* (5, 13, 39, 49). The data show that ICP27 can directly stimulate the translation of mRNAs to which it is bound and establish that ICP27 is sufficient to stimulate translation in the absence of any other viral factors (21). Moreover, Fontaine-Rodriguez *et al*. has showed that the interaction of ICP27 with translation factors are required for efficient translation of specific viral mRNAs (10), and they also confirmed that ICP27 stimulates translation of VP16 mRNA as well as an additional HSV-1 late ICP5 mRNA, and this function requires the C terminus of ICP27 (10). Ellison *et al*. also showed that ICP27 enhances VP16 expression primarily by increasing the translational efficiency of VP16 mRNA (9).

THE ROLE OF ICP27 IN VIRION COMPOSITION

HSV-1 virions are composed of four morphologically distinct structures: core, capsid, tegument, and envelope. Viral proteins that are present in the cell at the very earliest stages of infection have critical regulatory functions, e.g., to counteract host immunity or to transactivate viral gene expression. Recently, Sedlackova and Rice have showed that ICP27 plays a previously unrecognized role in determining the composition of HSV-1 virions (41).

ICP27 is a nucleocytoplasmic shuttling protein that performs a number of functions during infection, most notably the induction of several E and L viral genes (38, 42). ICP27 also determines the intracellular localization of ICP0 and ICP4. Furthermore, the mechanism by which ICP27 promotes ICP0/4 cytoplasmic localization does not require the environment of the infected cell or other viral factors (41). As both ICP0 and ICP4 are known to be minor virion components, Sedlackova and Rice used a viral ICP27 deletion mutant *d*3-4 to test the hypothesis that the cytoplasmic localization of these proteins is required for their incorporation into viral particles (41). Consistent with this conjecture, *d*3-4 virions were found to lack ICP0 in their tegument and to have greatly reduced levels of

ICP4. Thus, the cytoplasmic localization of ICP0 and ICP4 appears to be a prerequisite for the assembly of these important transcriptional regulatory proteins into viral particles. Moreover, their results show that ICP27 plays a previously unrecognized role in determining the composition of HSV-1 virions (41). Namely, the IE protein ICP27, itself not a virion protein, is a required cofactor for the efficient virion incorporation of ICP0 and ICP4. Given that ICP27 can promote the cytoplasmic accumulation of ICP0/4 even in the absence of infection, it is likely that ICP27's role in virion assembly is indirect, though the mechanism by which ICP27 promotes the cytoplasmic accumulation of ICP0/4 is unknown (41). Thus, it appears that ICP27 can affect the composition of both the tegument and envelope, but by apparently distinct mechanisms (41).

CONCLUSION

Herpes viruses are highly disseminated in nature. Herpes simplex virus type 1 is one of the most intensively investigated viruses. HSV-1 serves as models and tools for the study of translocation of proteins, membrane structure, gene regulation, gene therapy, cancer therapy and so on. ICP27, conserved in all mammalian and avian herpes viruses, is a multifunctional regulatory protein that is required for HSV-1 productive infection. It is responsible for both repression and trans-activation of viral gene expression, depending on the target gene, at a post-transcriptional level. ICP27 protein is involved in various steps of HSV-1 gene regulation and functions to shut off host protein synthesis by inhibiting the splicing of host pre-mRNAs, and promoting nuclear export of viral mRNAs. Recently, many novel functions performed by the ICP27 protein, including LMB resistance, inhibition of the type Ⅰ IFN signaling, regulation of the viral mRNA translation and determining the composition of HSV-1 virions, were reported. Understanding the mechanism of the multifunctional regulatory protein ICP27 may advance our knowledge of the HSV-1 and promote the exploitation of efficient methods for prevent viral infection and antiviral therapy.

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