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REVIEW

Infected cell protein 0 functional domains and their coordination in herpes simplex virus replication

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Abstract

Herpes simplex virus 1 (HSV-1) is a ubiquitous human pathogen that establishes latent infection in ganglia neurons. Its unique life cycle requires a balanced "conquer and compromise" strategy to deal with the host anti-viral defenses. One of HSV-1 α (immediate early) gene products, infected cell protein 0 (ICP0), is a multifunctional protein that interacts with and modulates a wide range of cellular defensive pathways. These pathways may locate in different cell compartments, which then migrate or exchange factors upon stimulation, for the purpose of a concerted and effective defense. ICP0 is able to simultaneously attack multiple host pathways by either degrading key restrictive factors or modifying repressive complexes. This is a viral protein that contains an E3 ubiquitin ligase, translocates among different cell compartments and interacts with major defensive complexes. The multiple functional domains of ICP0 can work independently and at the same time coordinate with each other. Dissecting the functional domains of ICP0 and delineating the coordination of these domains will help us understand HSV-1 pathogenicity as well as host defense mechanisms. This article focuses on describing individual ICP0 domains, their biochemical properties and their implication in HSV-1 infection. By putting individual domain functions back into the picture of host anti-viral defense network, this review seeks to elaborate the complex interactions between HSV-1 and its host.

Key words: Subcellular translocation; Herpes simplex virus 1; Infected cell protein 0; E3 ubiquitin ligase; Protein modification; ND10 nuclear bodies; Chromatin repression

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Core tip: Due to the genomic limitation, viruses often use multifunctional proteins to ensure viral replication. Coordination of the multiple viral functions is critical for a successful viral infection. Infected cell protein 0 (ICP0) is notoriously multi-functional in terms of simultaneously targeting many host machineries located in different cellular compartments. Understanding the molecular basis of ICP0 multifunctionality is important for not only the elucidation of herpes simplex virus pathogenicity but also the delineation of host defense mechanisms.

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INTRODUCTION

Herpes simplex virus 1 (HSV-1) is a ubiquitous virus that infects over 70% of the world adult population. It causes a wide range of clinical manifestations, including cold sores, genital ulceration, keratitis, and herpes encephalitis. Once infected, HSV-1 establishes a lifelong latency in human trigeminal ganglia. Its sporadic reactivation nourishes a wide spread of the virus. It is one of the most prevalent opportunistic pathogens that can cause severe diseases in newborns or immunocompromised patients. Infected cell protein 0 (ICP0), an α (immediate early, IE) gene product of HSV-1, is a key regulator that activates viral gene expression in both lytic and latent infections[1]. This multifunctional protein plays a critical role in viral counteractions against the host anti-viral defenses.

In early studies, viral proteins expressed in HSV-1 infection were classified into two groups: Virion proteins and infected cell proteins (ICPs)[2]. Both groups were numbered in the order of their descending molecular weight, with number "1" representing the largest protein on high resolution polyacrylamide gels[2]. ICP0 was named outside of the natural numbers for two reasons. First, the protein level of ICP0 was significantly lower than other ICPs. ICP0 was not detected in the initial efforts of numbering the ICPs[2]. It was only discovered after a cycloheximide treatment, which augmented mRNA accumulation and boosted a sudden protein production following the cycloheximide withdrawal[3]. The second reason why ICP0 was named differently was its anomalous mobility in denaturing polyacrylamide gel electrophoresis. The relative position of ICP0 *vs* other ICPs was not consistent on gels with different acrylamide concentrations, which made it impossible to give ICP0 a fixed position in the descending order of molecular weight.

Later on ICP0 was found to be extensively post-translationally modified[4-8] and to undergo quick turnover at early infection[9,10]. The complex biochemical properties of ICP0 likely contribute to the aforementioned low abundancy and abnormal mobility. Three decades of studies have showed that ICP0 is an important viral multifunctional protein to counteract against host anti-viral defenses. It is essential for low multiplicity infection in cultured cells and for latency reactivation in animal models. However, the complexity of how ICP0 carries out those biological functions is not well understood. Understanding the biochemical foundations of ICP0 at different infection phases will help to elucidate the molecular basis of ICP0 functionality. Individual functions of ICP0 as E3 ubiquitin ligase or chromatin remodeler have been discussed elsewhere[11-16]. This review will focus on dissecting ICP0 biochemical properties and seek to understand the profound coordination in the multiple functions of ICP0.

THE TIMELINE OF REVEALING ICP0 ACTIVITIES, A BRIEF HISTORICAL OVERVIEW

Initially, ICP0 was found to transactivate HSV-1 promoters when co-transfected in mammalian cells, similar to many other IE viral proteins such as ICP4 of HSV[17,18], T antigen of SV40[19], and E1A of adenovirus[20]. However, it was quickly realized that the mechanism of ICP0 transactivation was quite different from that of other viral gene activators. For example, ICP4 is essential for viral replication. Deletion of ICP4 led to abnormal viral expression and defective DNA replication[21,22]. In the case of ICP0, gene deletion did not affect viral expression or DNA replication at high multiplicity of infection (MOI) but it had great impact on the viral yield when MOI was lower than 0.1[23]. In experimental animals, deletion of ICP0 mildly reduced the efficiency of latency establishment but completely abolished the latency reactivation[24], whereas ICP4 or ICP27 deletion rendered the mutant virus neither able to replicate in the eyes nor to establish latent infection[24]. Moreover, many viral IE proteins contain a DNA binding domain and they work in mechanisms similar to cognate transcription activators such as GAL4, but ICP0 did not bind to the DNAs it activated[25,26]. Extensive functional analysis showed that ICP0 can transactivate a wide range of cellular promoters or promoters from other DNA or RNA viruses, with no requirement of a specific *cis*-sequence[27-29]. Therefore, ICP0 is defined as a promiscuous transactivator.

The unique functionality of ICP0 energized a great amount of interests in the virology field. In early 1990s, a series of mutagenesis analyses identified a cysteine-rich region required for the ICP0 transactivation activity[30-32], which was later determined as a C3HC4 zinc binding really interesting new gene (*RING*) finger motif[33-35]. Conserved RING finger sequences were found in a large family of E3 ubiquitin ligases[36,37]. Later on, ICP0 was also proven to be an E3 ubiquitin ligase[38,39]. The discovery that various ICP0 substrates imposed restrictions on viral expression in the absence of ICP0[40-45] eventually led to a conclusion that one major function of ICP0 is to target host defensive molecules for ubiquitin-mediated proteasomal degradation. By degrading the restrictive host factors, ICP0 alleviates host defense and promotes viral gene expression.

Starting in the late 1990s, several labs made the efforts to identify ICP0 interacting proteins. From pull-down assays, yeast-2-hybrid screenings and coimmuno-

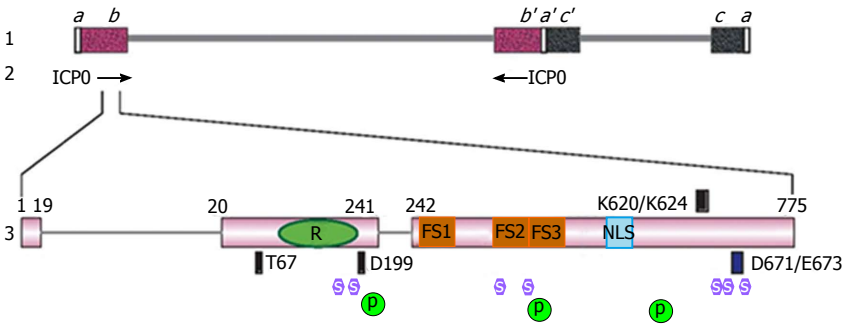

Figure 1 Schematic diagram of infected cell protein 0 gene structure and functional domains. Line 1: Genome structure of HSV-1; Line 2: Locations of the two inverted copies of ICP0 gene in the HSV-1 genome; Line 3: *ICP0* gene structure and domain properties. The amino acid numbers are labeled above the illustration of *ICP0* gene. RING finger domain, Proline-rich ND10-FSs and nuclear localization signal are represented by a green oval with "R", brown squares with "FS" and a blue rectangle with "NLS", respectively. The binding sites for RNF8 (T67), Cyclin D3 (D199), USP7 (K620/K624), and CoREST (D671/E673) are represented by the dark blue boxes above or beneath the *ICP0* gene. The positions of the seven SLSs are represented by lavender hexagons with "S" in the center. The positions of the three phosphorylation clusters are represented by dark green circles with "P" in the center. ICP0: Infected cell protein 0; HSV-1: Herpes simplex virus 1; RING: Really interesting new gene; ND10: Nuclear domains 10; NLS: Nuclear localization signal; USP7: Ubiquitin-specific protease 7; SLSs: SIM-like sequences.

precipitations, a wide range of cellular proteins were found to interact with ICP0[46-49]. Therefore ICP0 carries out viral counteractions by degrading restrictive factors and modulating repressive complexes, and consequently ICP0 enhances viral expression and replication. To better understand the coordination of ICP0 functional domains in counteracting host defenses, this review summarizes the current knowledge of ICP0 domains and ICP0 binding partners, and discusses their implications in HSV-1 infection.

ICP0 GENE STRUCTURE

The gene that encodes for ICP0 protein, also called *α0* gene, is located within the inverted sequences *ab* and *b′a′* that flank the unique long (U_L) region[50] (Figure 1). Therefore, the *ICP0* gene is one of the few HSV-1 genes that are diploid in the genome. The *ICP0* gene is also among the few HSV-1 genes that contain introns[51]. There are two introns of 765 and 136 nucleotides, respectively, intervening the three exons that encode for ICP0 amino acids 1-19, 20-241 and 242-775[51]. It is quite curious why the *ICP0* gene would evolve to bear introns because these introns do not seem to have significant functions in viral replication and alternative splicing of ICP0 has not been observed in infected cells. In one report, the ICP0 cDNA virus had a slight delay of gene expression depending on the cell-type used[52], whereas in another report differences between wild type virus and ICP0 cDNA viruses were not observed[53]. In animal models, recombinant viruses containing ICP0 deleted of introns showed no obvious defects in latency establishment and reactivation[54].

There is an in-frame stop codon located inside intron 2, which predicts a truncated form of ICP0 (ICP0R) if alternative splicing occurs. Overexpression of ICP0R inhibited the transactivation activity of the co-transfected wild type ICP0[55,56], suggesting ICP0R can work as a dominant negative to repress ICP0 activity. Although a band at the size of ICP0R was detected at low level in some cell lines[57], it remains unclear whether this is a product from alternative splicing or a product of proteolytic cleavage of ICP0. The function of ICP0R in the infection context is unknown.

One important fact about the *ICP0* gene is that the coding strand of ICP0 is anti-sense to the latency-associated transcript (LAT), the only transcript that is abundantly expressed in latently infected ganglia neurons[58,59]. The concept of LAT functioning as the anti-sense RNA to ICP0 mRNA has been explored and microRNAs identified in the LAT region have been shown to regulate ICP0 expression. Likely these actions fine-tune the basal level expression in latency maintenance and reactivation[60-62].

ICP0 PROTEIN: DOMAINS AND FUNCTIONS

RING finger domain and E3 ubiquitin ligase activity

The three exons of *ICP0* gene encodes for a 775-amino acid protein. It contains many functional domains and interacts with multiple binding partners (Table 1). The most important functional domain of ICP0 is the aforementioned C3HC4 zinc containing RING finger, which is located within exon 2 and spans through residues 116-156[63] (Figure 1). The promiscuous transactivator ability of ICP0 relies on a functional RING finger domain. Deletions or mutations of the consensus cysteine or histidine in the RING finger domain completely abolish the transactivation activity[63,64]. Recombinant viruses containing such deletions or mutations replicate at a rate similar to that of the ICP0-null virus[53,63,65]. This region is highly conserved among α-herpesviruses[34,63]. The structure of ICP0 RING finger has been solved by nuclear magnetic resonance (NMR)[35].

The RING finger domain of ICP0, like many RING superfamily members[36,66,67], works as an E3 ubiquitin ligase. Mediated by the E2 conjugating enzyme UbcH5a[68,69], ICP0 uses this domain to ubiquitinate its

Table 1 Infected cell protein 0 functional domains

Domain	Location	Function in HSV-1 replication	Section	Ref.
ICP0 cis-elements				
RING finger	aa 116-156	E3 ubiquitin ligase, degrading PML, Sp100, *etc.*	RING finger domain and E3 ubiquitin ligase activity	[63-65]
Proline-rich region	aa 241-553	Containing redundant ND10-fusion segments	Proline-rich region and ND10-fusion	[105]
NLS	aa 500-506	Nuclear localization	Nuclear localization domain and ICP0 nuclear/cytoplasmic translocation	[90]
Dimerization domain	aa 617-711	ICP0 self-dimerization, *in vivo* functions unclear	Dimerization	[115-117]
ND10-retention domain	aa 669-775	Retaining ICP0 at ND10	ND10-retention	[53]
SLSs			SUMO interaction motif and ICP0 substrate recognition	[113]
SLS-4	aa 361-367	Binding to SUMO-1/2/3, stimulating *in vitro* polyubiquitination		
SLS-5, SLS-7	aa 651-655, 681-685	Binding to SUMO-1, cooperating with SLS-4		
ICP0 binding partners				
RNF8	T67	Degrading RNF8 to regulate DNA damage responses	RNF8	[42,43]
Cyclin D3	D199	Involved in nuclear-to-cytoplasmic translocation of ICP0	Cyclin D3	[46,133-135]
BMAL1	aa 20-241	Activating viral transcription *via* BMAL1/CLOCK	BMAL1	[48,140]
EF-1δ	aa 543-768	Inhibiting translation *in vitro*, *in vivo* functions unclear	EF-1δ interaction	[96]
USP7	K620/K624	USP7 degradation, Cell-dependent ICP0 stabilization,	USP7 interaction	[47,85,88,123]
CoREST	D671/E673	Dislodging HDAC from REST/CoREST/HDAC repressor	CoREST interaction	[49,124]
WDR11	N/A	Regulating virion assembly and egress	WD repeat protein 11	[143]

ICP0: Infected cell protein 0; HSV-1: Herpes simplex virus 1; RING: Really interesting new gene; ND10: Nuclear domains 10; PML: Promyelocytic leukemia; Sp100: Speckled 100 kDa; NLS: Nuclear localization signal; SLS: SIM-like sequence; BMAL1: Brain and muscle ARNT-like protein 1; EF-1δ: Elongation factor 1δ; USP7: Ubiquitin-specific protease 7; SUMO: Small ubiquitin-like modifier; CLOCK: Circadian locomotor output cycles kaput.

substrate proteins and targets them for proteasomal degradation. The first two ICP0 substrates, promyelocytic leukemia (PML) and Sp100 (speckled 100 kDa) were identified by Chelbi-Alix and de Thé[40]. PML and Sp100 are the major organizer proteins for the dynamic nuclear bodies called nuclear domains 10 (ND10s) or PML nuclear bodies (for reviews, see references[70,71]). ND10s are nuclear structures that are composed of over 150 constituents[72]. They are involved in many cellular functions including gene regulation[73,74], cell cycle arrest[75], apoptosis[76], DNA repair[77] and anti-viral defense[78]. Degradation of PML and Sp100 by ICP0 leads to the dispersal of ND10 bodies[79]. In ICP0-null virus infection, depletion of PML and Sp100 was shown to compensate for the loss of ICP0 and to increase viral replication[41,80]. In $PML^{-/-}$ mouse embryotic fibroblasts (MEF), interferon (IFN) caused minimal effects on low multiplicity HSV-1 infection, whereas IFN treatment of $PML^{+/+}$ MEF reduced viral growth at least 1000 folds[81], suggesting that PML can mediate the IFN inhibition on viral replication. Taken together, PML is an important factor in host defense pathways and ICP0 targets PML, and maybe also Sp100, to alleviate anti-viral repressions.

Additional ICP0 substrates identified up to date include DNA-dependent protein kinase K (DNAPK)[82], centromeric proteins C and A (CENP-C and CENP-A)[83,84], ubiquitin-specific protease 7 (USP7)[85], RNF8[43], the 111-kDa isoform of poly (ADP-Ribose) glycohydrolase[86], interferon inducible protein 16 (IFI16)[44], and tripartite motif (TRIM) protein TRIM27[87]. Among these substrates, siRNA knock-down of RNF8 or IFI16 promoted the replication of ICP0-null virus[43,45], suggesting the involvement of these two proteins in host anti-viral defenses. However, depletion of TRIM27 reduced the viral yield in the absence of ICP0[87], and overexpression of USP7 accelerated gene expression in wild type HSV-1 infection[88]. These results indicate that not all ICP0 substrates place simple direct repressions on viral gene expression. Some of the substrate proteins may be degraded to regulate a more complicated cell network in order to benefit the overall viral outcome, especially the balanced actions in latent infection.

The E3 ubiquitin ligase activity of ICP0 RING finger is highly regulated by multiple factors, including its subcellular location, its phosphorylation status, and its other functional domains. For example, a failure of ICP0 to completely merge with ND10 bodies blocked substrate access and abolished PML degradation[53], and two amino acid substitutions in the C-terminal CoREST binding site (D671A/E673A) also negatively affected PML degradation[89]. The regulatory mechanisms of ICP0 E3 are not completely understood. Some of the known regulations will be discussed more in detail as we describe other important ICP0 properties in this review.

Nuclear localization domain and ICP0 nuclear/ cytoplasmic translocation

ICP0 contains a nuclear localization signal (NLS) mapped to the short stretch of basic amino acids VRPRKRR located at residues 500-506[90] (Figure 1). This arginine-rich NLS is sufficient and necessary for the nuclear localization of transiently transfected ICP0[90]. However, in infected cells, ICP0 is not an exclusively nuclear protein. Its subcellular distribution is regulated by many other factors in addition to the NLS.

First of all, ICP0 undergoes localization changes during the infection process. Early in infection, newly synthesized ICP0 is immediately transported into the nucleus in the presence of the NLS. Once inside the nucleus, ICP0 is immediately localized to the dynamic nuclear structure ND10[91]. This leads to the aforementioned degradation of ND10 organizers, PML and Sp100[40], and the subsequent disruption of ND10 nuclear bodies[79]. The dynamic interaction between ICP0 and ND10 is critical for the efficient access of ICP0 to its substrates, PML and Sp100, and their subsequent degradation[53], which will be discussed in depth in section "Proline-rich region and ND10-fusion".

After the dispersal of ND10 bodies, ICP0 diffuses throughout the nucleus. Once its nuclear functions are completed, ICP0 is translocated into the cytoplasm[92,93]. Many important ICP0 functions are carried out in the nucleus, where ICP0 degrades PML and interacts with REST/CoREST chromatin repressor (see section "CoREST interaction") early in infection. Pre-transfection of irrelevant DNA before infection can prolong ICP0 nuclear localization and delay the cytoplasmic translocation, especially in cell lines that poorly express transgenes[93]. These results suggest that ICP0 is kept within the nucleus until its nuclear functions are completed[93].

It is not yet clear how the NLS containing ICP0 protein is translocated into the cytoplasm at late infection. Either the NLS is modified late in infection so that newly translated ICP0 cannot enter the nucleus, or a nuclear export signal (NES) is unmasked late in infection so that nuclear ICP0 is exported. So far, a functional NES has not been identified.

Multiple viral factors have been found to participate in regulating the nuclear-to-cytoplasmic translocation of ICP0. For example, deletion of ICP4 caused ICP0 to lose its nuclear localization. Even at early infection, ICP0 expressed in the ICP4-null virus infected cell was solely found in the cytoplasm[94]. On the other hand, deletion of ICP27 retained ICP0 within nucleus throughout the infection and overexpression of ICP27 facilitated ICP0 export into the cytoplasm[94]. Since ICP27 is highly expressed in ICP4-null virus infected cells, ICP27 is likely the factor promoting ICP0 export. Another viral protein, VP22, has also been reported to play a role in the ICP0 cytoplasmic translocation. Deletion or mutation in VP22 restricted a series of viral proteins, including ICP0, inside the nucleus[95]. Whether or not VP22 affects a general nuclear export pathway and therefore indirectly delays ICP0 translocation remains unclear.

Functions of cytoplasmic ICP0 are not understood either. Kawaguchi *et al*[96] reported an interaction between ICP0 and translation elongation factor 1δ (EF-1δ) (also see in section "EF1δ interaction") and showed that ICP0 inhibited *in vitro* translation *via* this interaction. However, regulation of cellular translation by ICP0 is yet to be seen *in vivo*. Paladino *et al*[97] showed that ICP0 lacking NLS stayed in the cytoplasm and blocked IRF3 activation in infected cells. It remains unknown whether ICP0 directly interacts with IRF3 or secondary mediators are involved in this inhibition. Small amount of ICP0 has also been found in the tegument of purified virions[98,99]. Although the function of virion-associated ICP0 is not clear, it has been reported that ICP27 dependent cytoplasmic translocation of ICP0 is required for the incorporation of ICP0 into virions[100]. Delboy *et al*[101,102] also showed that an active ubiquitination was important for ICP0 to be incorporated into virions. Both RING finger mutation and proteasome inhibition precluded ICP0 from associating with virions. Since defective ubiquitination sequesters ICP0 within the ND10 bodies and prevents the cytoplasmic translocation of ICP0[89,92], Nicola's results are consistent with the observation that cytoplasmic localization of ICP0 in late infection is a prerequisite for the incorporation of ICP0 into virions. Since up to 49 cellular proteins have also been found in purified virions[99], the selection mechanism of low copy tegument proteins and their biological significance are not clear.

Proline-rich region and ND10-fusion

In the center of ICP0 protein, there is a long stretch of proline-rich region spanning residues 241 to 553. Initial deletion mapping found that serial deletions from the carboxyl-end of this region resulted in a progressive loss of the ICP0 transactivator activity[55], indicating the importance of this region in ICP0 functions. Multiple repeats of the PxxP motif in this region can interact with the Src homology 3 (SH3) domain in Cbl-interacting protein 85 kDa (CIN85), and a few other Src kinase family members[103,104]. Recently, Zheng *et al*[105] demonstrated that the proline-rich sequences were important to direct the fusion of ICP0 with ND10 nuclear bodies. As discussed above, ICP0 is localized to ND10 at early infection. This colocalization process is composed of three sequential dynamic steps: ND10-adhesion, ND10-fusion and ND10-retention[53]. Among these steps, a successful ICP0-ND10 fusion is essential for the ICP0 E3 ligase to access and degrade its substrate PML[53]. The proline-rich region of ICP0 is critical for the ND10-fusion step[105]. Zheng *et al*[105] showed that three proline-rich segments located at residues 242-291, 343-391, and 393-441, termed ND10-FS1, ND10-FS2 and ND10-FS3, respectively (Figure 1), redundantly facilitated the ND10-fusion of ICP0. Deletion of one or two ND10-FSs did not substantially affect the fusion process. However when all three ND10-FSs were deleted, ICP0 was blocked from entering the ND10 bodies[105]. Since most

of the cellular PML is located at ND10, the ICP0-ND10 fusion ensures a quick access of ICP0 to large amount of substrate and leads to an effective PML degradation. This likely increases the efficiency of ICP0 destroying the host restrictive factor PML and therefore enhances gene expression. The redundancy in proline-rich segments indicates the importance of ND10-fusion process in HSV-1 infection. Whether the redundant ND10-FSs synergistically improve the speed of ND10 fusion is a very important question waiting to be answered. It is also unknown whether ND10-FSs work *via* interacting with a SH3 domain or other proline-interacting motifs.

Small ubiquitin-like modifier interaction motif and ICP0 substrate recognition

Small ubiquitin-like modifier (SUMO) is a unique type of post-translational modification found on a variety of proteins. Protein SUMOylation functions in almost every aspect of a cell's life, including cell cycle, genome integrity, subcellular transport, and host immune defenses (for reviews, see references[15,106-108]). The SUMO moiety is recognized by hydrophobic sequences called the SUMO-interaction motif (SIM)[109,110]. RING-type E3 ubiquitin ligases that contain a SIM and specifically recognize SUMOylated substrates are classified as SUMO-targeted ubiquitin ligases (STUBL)[111,112]. Boutell *et al*[113] identified seven putative SIM-like sequences (SLSs) scattering throughout the ICP0 open reading frame (Figure 1). In yeast-2-hybrid assays, mutations in SLS-4 abolished the interaction between ICP0 and SUMO-2/3, whereas mutations in SLS-5 and SLS-7 did not affect such binding. SLS-4 was also found to be necessary for the *in vitro* ubiquitination of a SUMO-2 chain, indicating that ICP0 can work as a STUbL to preferentially recognize SUMOylated proteins for ubiquitination[113]. However, a recombinant virus containing mutant SLS-4 did not affect the degradation of endogenous PML in infected cells, while PML with all SUMOylation sites mutated were still degraded by ICP0[113], suggesting a more complex regulation on ICP0 substrate recognition in addition to the SUMO-SIM interaction. Moreover, although mutations in SLS-5 and SLS-7 did not interfere with the binding between ICP0 and SUMO-2/3, a recombinant virus carrying triple mutations in SLS-4/5/7 greatly demolished the ability of ICP0 to degrade PML[114]. This suggests there may be differences in the SLS affinities and multiple SLSs may work synergistically in PML degradation.

The C-terminus of ICP0 and a diverse array of functions

The C-terminus of ICP0, broadly defined for the region from downstream of NLS to the carboxyl-end, may be the most active but also the least understood region of ICP0. At least five major functions or interactions have been described in this region.

Dimerization: First, ICP0 is a protein known to aggregate and dimerize *in vitro* and *in vivo*[115-117]. In chromatography purification, ICP0 was fractionated at a much bigger molecular weight[117]. When wild type and mutant ICP0 were co-transfected into the same cell, the wild type ICP0 was able to correct the subcellular distribution of a mislocated mutant ICP0. The dimerization domain has been mapped to C-terminal residues 617-711[115]. The biological function of ICP0 dimerization is not yet clear.

ND10-retention: The second function of ICP0 C-terminus is related to the ND10 localization property of ICP0. Initial data showed that ICP0 lacking the C-terminus was evenly dispersed throughout the nucleus, compared to the full-length ICP0 that was colocalized to the ND10 bodies[117]. This led to an assumption that the C-terminus of ICP0 is responsible for ND10 localization[117,118]. However, recent results from Gu *et al*[53] showed that the C-terminus of ICP0 was not involved in the recruitment of ICP0 to ND10. In the absence of C-terminus, ICP0 did not aggregate at ND10 but had the ability to degrade PML. When a double mutant of both C-terminal truncation and RING finger mutation was introduced, ICP0 was found to localize at ND10. These results suggest that the C-truncated ICP0 undergoes adhesion and fusion steps to enter ND10, but it cycles in and out of ND10 in a more accelerated mode. Only when the inactive RING blocks the enzymatic reaction into a transition state, can the ICP0-ND10 colocalization be observed in a steady-state immunofluorescence staining. Therefore the C-terminus of ICP0 is responsible for the retention, but not the recruitment, of ICP0 to ND10.

USP7 interaction: The C-terminus of ICP0 also interacts with various proteins, such as USP7[47], CoREST[49] and EF-1δ[96], which are from proteasome pathway, chromatin repressor complex and translational machinery, respectively.

USP7 is the first ICP0 interacting protein identified *via* a GST pull-down/protein sequencing assay[47,119]. This is a deubiquitinase that regulates the ubiquitination status of many important cell check point proteins, such as p53[120], RE1-silencing transcription factor (REST)[121], and phosphatase and tensin homolog (PTEN)[122]. The minimum sequences required for the strong binding between the two are amino acids 615-633 of ICP0 and amino acids 535-889 of USP7[123]. The crystal structure of USP7 C-terminal ubiquitin-like domains bound with ICP0 peptide has been solved. Salt bridges between K620/K624 of ICP0 and D762/D764 of USP7 are critical for the interaction, while the peripheral residues form a binding pocket to support the strong ICP0-USP7 interaction[123]. Consistent structural data have also been obtained from NMR assays[124].

Initial *in vitro* ubiquitination assays showed that ICP0-USP7 interaction inhibited ICP0 autoubiquitination but promoted USP7 polyubiquitination[8,85]. Consistent with these observations, the ICP0-USP7 interaction was found essential for the degradation of USP7 by ICP0 in infected cells[85,88]. However, regarding to ICP0 autoubiquitination,

different groups have reported contradictory results[85,88]. Boutell *et al*[85] used HSV-1 (strain 17+) and reported that wild type ICP0 stayed at a steady level after cycloheximide treatment, whereas an R623L/K624I mutant virus, of which ICP0 was incapable of binding to USP7 and was quickly degraded in the presence of cycloheximide. On the other hand, Roizman and colleagues demonstrated that wild type ICP0 of HSV-1 (strain F) underwent rapid degradation at early infection and was only stabilized late in infection[9,10]. Furthermore, they found that a K620I mutant virus that abolished ICP0-USP7 interaction had enhanced, not reduced, viral gene expression but showed defects in plaque formation[88]. Therefore, ICP0-USP7 interaction may have profound biological significances, depending upon the virus strains and cell lines. Since both ICP0 and USP7 have a wide range of different substrates that are involved in critical cellular pathways, the interaction between ICP0 and USP7 may be more important in fine-tuning the ubiquitin status of these check point proteins than simply regulating ICP0 self-stability. A complex balance of these proteins may in return affect ICP0 stability in a cell type dependent manner.

CoREST interaction: CoREST binding to ICP0 was discovered by co-immunoprecipitation[125]. CoREST is the corepressor partner for REST[126]. REST/CoREST are the key components of a chromatin regulatory complex that determines neural cell fate during development[127]. The CoREST binding of ICP0 is mapped to the amino acids D671/E673[89]. Gu *et al*[125] showed that ICP0-CoREST interaction depended on the presence of viral kinases U_S3 and U_L13, and a prolonged infection resulted in less binding, suggesting that ICP0-CoREST interaction is a regulated transient process. This interaction was found essential for the dissociation of HDAC1 from REST/CoREST complex in HSV-1 infection[89,125]. A recombinant virus carrying a dominant negative CoREST incapable of HDAC1-binding showed a higher viral productivity in the absence of ICP0, which means the disruption of HDAC1-CoREST interaction is beneficial for viral replication[49]. Furthermore, on the molecular level, a recombinant virus containing D671A/E673A mutations had less acetylated histone H3 compared with the wild type virus or a mutant virus that kept the effective ICP0-CoREST interaction[128]. In contrast to these results, Everett showed that depletion of CoREST did not improve the yield of ICP0-null virus[129]. The seemingly contradictory results are reconciled from the fact that lysine-specific demethylase-1 (LSD1), another important component in the REST/CoREST complex, is required in HSV-1 replication[130]. Therefore the stoichiometry of REST/CoREST/LSD1/HDAC components[127] may play a role in determining the interaction to different viral proteins at different infection phases.

EF1δ interaction: Interaction between ICP0 and EF-1δ was identified through a yeast-2-hybrid screening[96]. The binding has been mapped to the C-terminal residues 543-768 and found to inhibit *in vitro* translation[96]. However, *in vivo* function of this interaction is not clear.

For all these different C-terminal functions it is not clear how these seemingly unrelated activities coordinate in this region. Are there different subsets of ICP0 distributed in distinct subcellular compartments? Or some of the components from different pathways converge at certain cellular hubs, such as ND10? Answers to these questions will be the key to understanding the complex functions of ICP0 in both lytic and latent infections.

Other ICP0 interaction partners

Cyclin D3: Cyclin D3 is identified as an ICP0-interacting protein by a yeast-2-hybrid screening[46]. D-type cyclins form complexes with cyclin-dependent kinases to regulate G1 to S phase transition[131,132], which can be manipulated by many DNA viruses for the purpose of promoting DNA synthesis in infected cells[133]. ICP0 interacts with Cyclin D3 through its amino acid D199 located in exon 2, downstream to the RING finger domain (Figure 1). The D199-Cyclin D3 interaction is important in the nuclear-to-cytoplasmic translocation of ICP0. Mutation in cyclin D3 binding site or treatment by CDK4 inhibitor during the infection prevented ICP0 from translocating to the cytoplasm[134,135], whereas insertion of cyclin D3 gene into the HSV-1 genome to overexpress cyclin D3 led to an accelerated cytoplasmic translocation[135,136]. The regulation of the cell cycle during HSV-1 infection is a profound event involving multiple factors. For example, HSV-1 ICP22 and U_L13 are found to participate in G2/M transition[137], and CDK inhibitor roscovitine inhibits HSV-1 gene transcription without affecting PML degradation[138,139]. Moreover, the D199 dependent nuclear-to-cytoplasmic translocation of ICP0 is a process that depends on viral DNA replication and the expression of a late protein(s)[92]. Therefore different cell cycle regulatory pathways are interwoven with ICP0 phosphorylation, translocation and possibly other infection events. The concerted efforts from both viral and cellular sides determine the ultimate productivity of an HSV-1 infection.

Brain and muscle ARNT-like protein 1: Brain and muscle ARNT-like protein 1 (BMAL1) interacting with ICP0 is also identified by a yeast-2-hybrid screening[48]. The interaction site to BMAL1 is located in the exon 2 of ICP0[48]. BMAL1 and circadian locomotor output cycles kaput (CLOCK), a histone acetyltransferase, forms a heterodimer to regulate mammalian circadian oscillation[140]. During HSV-1 infection, CLOCK is stabilized and recruited to ND10, which acts as a transcription activator to stimulate viral transcription and replication[141].

RNF8: The identification of ICP0-RNF8 interaction was based on the observation that RNF8 was degraded by ICP0 in HSV-1 infection[42,43]. RNF8 is an RING type E3 ubiquitin ligase that plays a key role in histone ubiquitination and chromatin remodeling upon DNA double-

stranded break (DBS) damage[142,143]. ICP0-RNF8 binding is mapped to the phosphorylated amino acid T67 of ICP0, and amino acid R42 of RNF8[43]. A recombinant virus carrying the T67A mutation did not degrade RNF8 but had no problems in degrading DNAPK or USP7, which means ICP0-RNF8 interaction is likely important for a specific RNF8 substrate recognition[43]. Interestingly, knock-down of RNF8 only mildly delayed *ICP27* gene transcription and had no effects on viral DNA replication, suggesting that the involvement of ICP0-RNF8 interaction in responding to DBS DNA damage is, again, a complex action.

WD repeat protein 11: WD repeat protein 11 (WDR11) is a newly reported ICP0 interacting protein identified by co-immunoprecipitation[144]. Taylor *et al*[144] showed that the trans-Golgi network localized WDR11 pulled down several viral proteins including gB, VP16 and VP5 in additional to ICP0, suggesting its possible role in virion assembly and egress.

POST-TRANSLATIONAL PROCESSING OF ICP0

Modification

ICP0 protein contains 775 amino acids, but the apparent molecular weight of ICP0 is about 110 kDa[3], suggesting the presence of post-translational modifications for ICP0. First of all, ICP0 is highly phosphorylated. On two-dimensional gel electrophoreses, ICP0 phosphorylation status changes along with the progression of infection[6]. The phosphorylation sites on ICP0 has been mapped to three phosphor-clusters by tandem mass spectrometry. Cluster 1 is at residues 222-250, cluster 2 is at residues 356-386, and duster 3 is at residues 505-528[145] (Figure 1). Davido and colleagues showed that serine/threonine mutations in these clusters demolished the transactivation activity of ICP0 and reduced the viral replication in mice[145,146]. Viral protein U_L13 was found important for ICP0 phosphorylation[147]. However, how ICP0 phosphorylation coordinates with ICP0 localizations or ICP0 protein-protein interactions to affect the infection is not yet known.

Other modifications of ICP0 are understudied. ICP0 is believed to be nucleotidylated because it can be radiolabeled in infected cells cultured with [α-^{32}P]GTP or [2-^{3}H]ATP containing medium[5]. ICP0 may also be ubiquitinated because it is found to autoubiquitinate itself in *in vitro* polyubiquitination assays[8].

Proteolytic cleavage and rapid turnover

At least in the infection of HSV-1 (strain F), ICP0 undergoes a rapid degradation at early infection in both proteasome dependent and proteasome independent manners. The protein is then stabilized at late infection[9]. The proteasome independent cleavage occurs in the central region of ICP0 and the rapid turnover depends on the *cis* presence of an active RING finger as well as the phosphorylation status of ICP0[9,10].

CONCLUSION

Like all herpesvirus family members, HSV-1 establishes latent infection. The peculiar life cycle of HSV-1 necessitates a close interaction and a delicate balance between the virus and its host. ICP0 of HSV-1, a unique multifunctional protein, plays a key regulatory role to enhance gene expression in lytic infection and to reactivate virion production from latent infection. This protein is tightly regulated on transcriptional, post-transcriptional and post-translational levels. Through its intrinsic functional domains and its ability to interact with a wide range of binding partners, ICP0 can target many cellular protein for proteasomal degradation and regulate various cell pathways *via* protein-protein interactions.

To achieve its multiple functions, ICP0 undergoes modification and subcellular translocation. Early in infection, ICP0 is immediately imported into the nucleus upon synthesis. Once inside the nucleus, it is recruited to adhere at and then fuse with ND10 to co-mingle with ND10 components. The ND10-fusion process ensures ICP0 to quickly access large amounts of PML and Sp100 for degradation and to extensively interact with many of the regulatory factors located within ND10. This early step in HSV-1 infection is vital for the outcome of a productive infection, not only by destroying and dispersing the repressive factors but also by capturing favorable factors that help establishing replication compartment. Upon viral DNA entering the nucleus, host cell attempt to silence the foreign intrusion by: (1) forming ND10 bodies near viral DNA[148]; (2) recruiting chromatin repressors[149]; and (3) stimulating IFN responses[45]. In a way, HSV-1 deploys ICP0 to approach ND10 is a "smart" move because ND10 serves as a molecular hub for many cellular pathways and it is able to recruit component factors upon specific stimulations[78]. Therefore, adopting factors recruited to ND10 during infection while destroying and repelling restrictive components is an effective strategy to boost viral replication. In fact, various cellular check point proteins such as USP7, CoREST, Cyclin D3, BMAL1 and CLOCK are all recruited to ND10 upon infection and they are found in HSV-1 replication compartments[47,135,141,149]. In fact, HSV-1 replication compartments are established at the sites where ND10 loci have been located before their dispersal[149]. ICP0 interacting with the molecular hub ND10 is a major adaptation to coordinate the multitasking of ICP0 functions. Likely the sequential steps of ICP0-ND10 interaction, ND10-adhesion, ND10-fusion, ND10-retention[53], play important roles in achieving the "destroy and then take over" strategy.

Once the replication compartments are set up in the infected cells, ICP0 may have additional functions in a diffused pattern in nucleus and then in the cytoplasm. Whether the trafficking of ICP0 is regulated by post-translational modification or proteolytic processing is currently unknown. Solving the road map of ICP0 being in the right place at the right time will be a continuous

interest in the near future for herpes virology field.

ICP0 is required for latency reactivation[24]. The subtle balance of ICP0 level in latent infection may be achieved by microRNA regulation. The rapid turnover of ICP0 on the protein level may also be essential for the maintenance and reactivation of latent infection. After all, one good way to achieve massive spreading is to keep the sporadic but not severe recurrent infections.

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