Commentary

Interference in Innate Immunity: Another Dimension in ICP0 Multi-functionality

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Abstract | The literature regarding the ICP0 protein from herpes simplex virus is complex and frequently contradictory, meaning that although this protein has been implicated in a wide variety of diverse functions, the mechanisms through which it produces these effects continue to be elusive. Recent investigations into the ability of ICP0 to block the activation of antiviral signaling have revealed a potential explanation for some of this confusion – namely, that ICP0 has important functions in the cytoplasm that have been generally disregarded, due to the fact that many frequently used experimental manipulations restrict this protein to the nucleus. This commentary discusses the significance of these findings to the ICP0 field.

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Herpes simplex virus (HSV) is a tremendously successful human pathogen, with worldwide seroprevalence rates reaching 60%-90% (Smith and Robinson, 2002). The global conquest of this virus is due, at least in part, to its ability not only to produce a lytic infection of epithelial cells, but also to subsequently establish a latent reservoir in neurons, allowing it to escape immune surveillance while permitting it to persist and infect new individuals throughout the lifetime of the original host (reviewed in (Grinde, 2013)). As a large, complex double-stranded DNA virus, HSV encodes at least 84 proteins. Arguably, one of these proteins stands out among the rest, both in terms of importance to a large number of diverse viral functions as well as in its often perplexing behavior. This is the infected cell protein 0 (ICP0).

A survey of the literature quickly reveals the remarkable variety of activities in which ICP0 has been implicated, including roles in promoting lytic replication (Everett et al., 2004), promiscuous transactivation of both viral and cellular genes (Everett, 1984; Gelman and Silverstein, 1985; O'Hare and Hayward, 1985; Quinlan and Knipe, 1985), DNA template remodeling (Cliffe and Knipe, 2008; Coleman et al., 2008; Ferenczy and DeLuca, 2009; Kalamvoki and Roizman, 2010; Orzalli et al., 2013), capsid transport (Delboy et al., 2010), interference with the DNA-damage response (Lees-Miller et al., 1996; Parkinson et al., 1999; Li et al., 2008; Lilley et al., 2010; Chaurushiya et al., 2012), and disruption of both the centromere (Everett et al., 1999; Lomonte et al., 2001) and the cellular microtubule network (Liu et al., 2010). The means through which ICP0 accomplishes these different tasks remains unclear, and in many cases, controversial. A feature of ICP0 that is much touted in the literature as being essential to all of its varied functions is its Really Interesting New Gene (RING) finger domain, which acts as an E3 ubiquitin ligase (Everett, 2000). Because ubiquitination has long been associated with proteasome-mediated degrada-

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tion, the various effects produced by ICP0 are generally thought to result from the loss of a particular cellular protein. Indeed, ICP0 is associated with the proteasome-dependent degradation of no less than 15 cellular targets (Everett et al., 1998; Chelbi-Alix and de The, 1999; Everett, Earnshaw et al., 1999; Parkinson, Lees-Miller et al., 1999; Lomonte, Sullivan et al., 2001; Boutell and Everett, 2003; Boutell et al., 2005; Diao et al., 2005; Kummer et al., 2007; Lilley, Chaurushiya et al., 2010; van Lint et al., 2010; Fukuyo et al., 2011; Orzalli et al., 2012; Lin et al., 2013). Recently, however, an appreciation has developed that not all ubiquitin chains target a protein for degradation – depending on the specific lysine residue used to link the ubiquitin monomers, "atypical" chains may instead have signalling roles unconnected to the proteasome (reviewed in (Behrends and Harper, 2011)). Interestingly, E3 ubiquitin ligases can form more than one linkage type (reviewed in (Ye and Rape, 2009; Behrends and Harper, 2011)), and the particular lysines involved in chains generated by ICP0 have not been identified.

ICP0 has also been implicated in combating innate antiviral signaling, although the exact significance and mechanism of this activity remains hotly contested. The classic interferon (IFN)-mediated antiviral response occurs when cellular pathogen recognition receptors (PRRs), such as the Toll-like receptors (TLRs) and the retinoic acid inducible gene I (RIG-I)-like receptors (RLRs), recognize viral components and activate transcription factors, including IFN regulatory factor 3 (IRF3) and nuclear factor kappa B (NFκB), which collectively cause the production of the soluble cytokine IFN. Binding of IFN to cell-surface receptors induces signal transduction pathways that ultimately result in the expression of hundreds of IFN stimulated genes (ISGs), which work together to block viral replication (reviewed in (Hertzog and Williams, 2013)). ICP0 has been found to be involved in mediating viral resistance to the effects of IFN (Mossman et al., 2000; Harle et al., 2002; Mossman and Smiley, 2002; Everett and Orr, 2009), via the degradation of the ISG promeylocytic leukemia protein (PML) (Chee et al., 2003), a component of specialized nuclear bodies known as nuclear domain 10 (ND10) (Grotzinger et al., 1996; Everett, Freemont et al., 1998). However, it has also been suggested that as opposed to being important in IFN-mediated signaling, ND10 components such as PML, Sp100, hDaxx and ATRX (Everett et al., 2006; Everett et al., 2008; Lukashchuk and Everett, 2010) instead form an intrinsic antiviral response, composed of constitutively expressed proteins that work to block viral activities in the absence of *de novo* protein production (reviewed in (Bieniasz, 2004)). Indeed, members of ND10 cooperatively inhibit ICP0-null viral replication (Everett, Rechter et al., 2006; Everett, Parada et al., 2008; Lukashchuk and Everett, 2010; Glass and Everett, 2013), possibly by sequestering viral genomes to prevent their transcription (Boutell et al., 2011; Glass and Everett, 2013), which ICP0 counteracts by blocking the recruitment of these proteins to the viral genome (Maul et al., 1993; Everett, Freemont et al., 1998; Chelbi-Alix and de The, 1999; Everett and Murray, 2005; Lukashchuk and Everett, 2010).

Perhaps the most contentious of all the functions of ICP0 is its role in inhibiting the initial production of IFN. For example, the ability of ICP0 to block the activation of NFκB after TLR stimulation has been reported by two independent groups – each of which proposed a distinct and opposing mechanism. The first found that ICP0 recruited the deubiquitinating enzyme USP7 to the cytoplasm to remove non-degradative, activating ubiquitin chains from adaptor proteins TRAF6 and IKK-γ, in a process that did not require the RING finger of ICP0 (Daubeuf et al., 2009), while the second demonstrated that TLR signaling was inhibited via the RING-dependent degradation of adaptor proteins MyD88 and Mal (van Lint, Murawski et al., 2010). ICP0 has additionally been found to decrease both IRF3 activation and ISG expression (Mossman, Saffran et al., 2000; Mossman et al., 2001; Eidson et al., 2002; Lin et al., 2004; Melroe et al., 2004; Melroe et al., 2007; Paladino et al., 2010; Orzalli, DeLuca et al., 2012). This was initially found to require both the RING finger domain and an active proteasome (Eidson, Hobbs et al., 2002; Lin, Noyce et al., 2004), initiating a vigorous search for a component of IRF3 signaling that is subject to ICP0-mediated degradation. However, no change in the protein levels of TBK-1, IKK-γ, CBP, DDX3 or HSP90 was found during HSV infection (Lin, Noyce et al., 2004; Paladino, Collins et al., 2010). An enhancement in IRF3 degradation by ICP0, as well as the sequestration and inactivation of nuclear IRF3, has been proposed, but the Sendai virus co-infection model used in these studies complicates interpretation of these data (Melroe, DeLuca et al., 2004; Melroe, Silva et al., 2007), and others have found no such effect on IRF3 levels in the context of a single HSV infection (Lin, Noyce

et al., 2004; Paladino, Collins et al., 2010). Another potential target is the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs), which is degraded by ICP0 (Lees-Miller, Long et al., 1996; Parkinson, Lees-Miller et al., 1999) and is also thought to be involved in the activation of IRF3 (Karpova et al., 2002; Ferguson et al., 2012) – but cells deficient in DNA-PKcs still produced ISGs after HSV infection (Noyce et al., 2006). Finally, ICP0 has been reported to target the nuclear DNA sensor IFI16 to the proteasome, blocking IRF3 activation (Orzalli, DeLuca et al., 2012), but the loss of IFI16 has also been observed during infection with an ICP0-null virus, suggesting an ICP0-independent mechanism is involved (Cuchet-Lourenco et al., 2013). Therefore, the search continues for the ICP0-mediated degradation of a component involved in antiviral signaling.

Recently, further investigation into the means through which ICP0 blocks the activation of IRF3 has brought to light a key issue, which not only impacts our understanding of the role of ICP0 in antiviral signaling, but also has repercussions for the entire ICP0 field. This advance came from the discovery that the localization of ICP0 is crucial to its ability to inhibit IRF3 (Paladino, Collins et al., 2010). Under normal circumstances, at early times post-infection, the nuclear localization signal (NLS) of ICP0 causes it to localize to the nucleus, but it later translocates to the cytoplasm (Everett, 1988; Everett and Maul, 1994; Maul and Everett, 1994; Kawaguchi et al., 1997; Lopez et al., 2001). However, a variety of experimental manipulations can cause ICP0 to become partially or completely restricted to the nucleus (Zhu et al., 1994; Lopez, Van Sant et al., 2001; Van Sant et al., 2001; Potel and Elliott, 2005; Kalamvoki and Roizman, 2008; Gu and Roizman, 2009; Kalamvoki and Roizman, 2009; Taylor et al., 2014) including proteasome inhibition, expression of exogenous ICP0 outside of the context of viral infection, and disruption of the RING finger domain. In consequence, many studies inadvertently analyze only the nuclear functions of ICP0. The danger of this oversight is clearly demonstrated by a report showing that ICP0 that has been restricted to the nucleus, via a single amino acid change or use of a proteasome inhibitor, is incapable of impairing the activation of IRF3 – but an NLS mutant of ICP0, which is found only in the cytoplasm, efficiently blocks antiviral signaling, even during proteasome inhibition (Paladino, Collins et al., 2010). Therefore, because the localization of ICP0 had not been examined, previous investigations had erroneously concluded that the proteasome was required for the antiviral-inhibiting actions of ICP0 (Eidson, Hobbs et al., 2002), while it was, in fact, the cytoplasmic localization that was essential, and not the action of the proteasome at all. Similarly, when wildtype ICP0 is expressed in the absence of all other viral proteins, which also results in its nuclear retention, it is incapable of blocking ISG expression (Everett and Orr, 2009), leading to the misleading assumption that ICP0 is not involved in impairing IRF3. Interestingly, the RING finger of ICP0 has also been suggested to be involved in preventing ISG expression (Lin, Noyce et al., 2004), and once again, disruption of the RING finger causes ICP0 nuclear restriction (Gu and Roizman, 2009; Taylor, Chew et al., 2014). Surprisingly, however, the generation of a cytoplasmic RING finger mutant of ICP0 revealed that the RING finger domain is truly essential for the ability of cytoplasmic ICP0 to disrupt antiviral signaling (Taylor, Chew et al., 2014). This suggests, for the first time, that the RING finger has proteasome-independent functions, potentially via the conjugation of an atypical ubiquitin chain to a protein involved in IRF3 activation. Although the exact target of such an atypical modification remains to be determined, the concept that the RING finger has activities that do not require the proteasome represents an important paradigm shift in ICP0 biology. Importantly, the cytoplasmic RING finger mutant also revealed that ICP0 in this location has a RING finger-independent ability to promote viral replication both *in vitro* and *in vivo* (Taylor, Chew et al., 2014). Because of the reliance on RING finger mutants that predominantly localize to the nucleus, both of these intriguing effects had been previously overlooked – emphasizing the importance of considering localization when studying the function of ICP0.

In conclusion, ICP0 is a multifaceted viral protein involved in many aspects of HSV replication, although consensus is lacking on the precise mechanisms through which it produces its effects. Recent advances in understanding how ICP0 influences antiviral signaling have potentially revealed a general explanation for these inconsistent results – the location of ICP0 is vital to its activities, but the influence of common experimental techniques on the localization of ICP0 is rarely considered. The finding that the RING finger of ICP0 has proteasome-independent effects in inhibiting innate immunity, as well as the fact that ICP0 can enhance viral replication without requiring

an intact RING domain, suggest that the functions of ICP0 go beyond the simple targeting of proteins for degradation, adding an exciting new dimension to this enigmatic viral protein.

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