The N-terminus of the HSV-1 E3 Ubiquitin Ligase ICP0 Stimulates Viral Replication and Gene Expression in Cells Exposed to Interferon-ß

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HSV-1 infects sensory neurons in humans and establishes lifelong latent infections, which can reactivate by stress stimuli. Among the first proteins to be expressed when HSV-1 infects a cell is infected cell protein 0 (ICP0). ICP0 is an E3 ubiquitin ligase that stimulates viral gene expression and enhances viral replication. ICP0 facilitates viral gene expression by impairing the antiviral effects of the cellular factor, interferon (IFN)-β. The mechanism(s) by which ICP0 impairs IFN-β restriction on HSV-1 replication remain largely unknown. Consequently, the purpose of the present study was to determine which domain(s) in ICP0 contribute to HSV-1 resistance to the antiviral effects of IFN-β. To identify one or more domains, a series of ICP0 truncation mutants was used to perform plaque reduction and gene expression assays in untreated cells and cells pretreated with IFN-β. We determined that the first 388 N-terminal amino acids of ICP0 confer significant resistance of HSV-1 to IFN-β while efficiently stimulating viral gene expression; specifically, amino acids from 312 to 388 are crucial for mediating this resistance. We hypothesize that this N-terminal domain of ICP0 plays a role in counteracting the IFN-β-induced restriction on viral replication through ICP0-host protein interactions. Overall, we conclude that the N-terminal half of ICP0 enables HSV-1 to resist an established IFN-β response with residues from 312 to 388 being required for this function.