

The IFI16 restriction factor cooperates with HCMV pUL83 to down-regulate UL54 gene expression and viral DNA synthesis.

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Introduction. During the early phase of human Cytomegalovirus (HCMV) infection, the Interferon-Inducible factor 16 (IFI16) behaves as a pattern recognition receptor (PRR) sensing viral DNA and triggering antiviral cytokine release. Later on, it restricts virus replication by down-regulating expression of viral genes committed to DNA synthesis including UL54 and UL44. These activities are modulated by viral proteins including pUL83, a tegument protein involved in viral evasion.

Materials and methods. To assess the interplay between IFI16 and pUL83 we employed human foreskin fibroblasts (HFF) infected with the wild type HCMV strain (v65Rev), the HCMV v65Stop lacking pUL83 expression, or the HCMV mutant virus (RV-VM1) expressing a pUL83 lacking the nuclear egression signal (NES).

Results. Here, we demonstrate that pUL83 interacts with IFI16 relieving its inhibitory activity on UL54 gene transcription. We also establish that, starting from 48 hours post-infection, IFI16 is stabilized and protected from degradation by pUL83 as observed infecting HFF with v65Rev or the v65Stop lacking pUL83 expression. Upon infection with the HCMV mutant virus RV-VM1 IFI16 is retained in the nucleus and does not migrate into the cytoplasm. Interestingly, accumulation of nuclear pUL83 prevents the formation of discrete puncta and dissipates aggregation of IFI16 filaments. We observe that IFI16 shows a half-life of less than 1h in the absence of pUL83 compared with 2h in the presence of pUL83 demonstrating that IFI16 is less stable in the absence of pUL83. Consistent with this, we observe restoration of IFI16 protein in v65Stop-infected cells compared to v65Rev-infected cells in presence of the proteasome inhibitor MG132.

Discussion and conclusions. Our results demonstrate a novel role for the pUL83 protein that stabilizes and protects IFI16 from proteasome degradation during HCMV infection and modulates suppression of UL54 gene activity.