Structural Basis of Interaction of Herpesvirus Proteins with the Deubiquitinase USP7.

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Ubiquitin Specific Protease 7 (USP7) has emerged as a key regulator of many cellular pathways, including those critical for oncogenesis. USP7 is a deubiquitinase that regulates the stability or localization of specific substrate proteins by cleaving ubiquitin from them. USP7 consists of an N-terminal TRAF-like domain (NTD), a catalytic domain and five C-terminal ubiquitin-like (CTD) domains. USP7 was discovered as a target of a herpesvirus protein and later shown to be manipulated by multiple proteins from several different herpesviruses, earning its alternative name of Herpesvirus Associated USP (HAUSP). EBNA1 is the only Epstein-Barr virus protein expressed in infected cells and has important roles in EBV latent infection. We previously showed that the EBNA1 protein uses an EGPS motif to bind strongly to the NTD and blocks USP7 stabilization of p53. Using a combination of pull-down, binding and structural studies, we recently identified that USP7 interacts with vIRF1 of Kaposi's sarcoma herpesvirus via the identical EGPS motif. These studies also demonstrated that vIRF1 destabilizes p53 by hijacking USP7 similar to what was previously observed with EBNA1. We mapped the interactions between USP7 and herpes simplex virus 1 ICP0 using a combination of GST pull-down and fluorescence polarization studies. We determined the crystal structure of the CTD domain with an ICP0 peptide and identified USP7 residues mediating the interaction with ICP0. We have identified mechanisms of USP7 substrate recognition by its NTD and CTD that are used by both viral and cellular proteins. Further details and analysis of the crystal structures will be presented.