**Abstract**

Human Cytomegalovirus (HCMV) is a ubiquitous β-herpesvirus that latently infects 60-90% of the adult population worldwide. HCMV infection causes serious morbidity and mortality in immunocompromised individuals and neonates. Modulation of innate immune signaling is critical for successful HCMV infection, and elucidating the mechanisms involved could provide novel points for therapeutic intervention. Our laboratory previously found that the HCMV tegument protein UL26 is necessary for high titer viral replication and sufficient to block cytokine-induced NFκB innate immune activity. The underlying mechanisms through which UL26 modulates immune activation and contributes to successful viral infection are unclear. To address this, we created a recombinant virus containing UL26 fused to a promiscuous biotin ligase which successfully tagged UL26 proximal proteins with biotin during infection. These proteins were identified by LC-MS/MS to generate a list of putative UL26-interacting proteins necessary for high titer viral replication. Our results show that UL26 interacts with several innate immune response factors including transcription factors STAT1-3 and protein inhibitor of activated STAT (PIAS) proteins. We predict this interaction to be a determinant of successful viral replication, either by repressing the canonical anti-viral immune response or hijacking STAT transcription factors to promote viral replication. To interrogate the role of STAT and PIAS proteins during HCMV infection, we used CRISPR Cas9 to generate a STAT3 knockout cell line and found that HCMV spread is significantly reduced in cells lacking STAT3. These preliminary data support the possibility that UL26 interacts with STAT3 to promote viral replication. Collectively, our results provide insight into the complex relationships between HCMV, UL26, and cellular intrinsic anti-viral defense proteins.