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Herpes Viral Protein Targets a Cellular WD Repeat Endosomal Protein to Downregulate T Lymphocyte Receptor Expression

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Herpesvirus saimiri Tip associates with Lck and downregulates Lck signal transduction. Here we demonstrate that Tip targets a lysosomal protein p80, which consists of an N-terminal WD repeat domain and a C-terminal coiled-coil domain. Interaction of Tip with p80 facilitated lysosomal vesicle formation and subsequent recruitment of Lck into the lysosomes for degradation. Consequently, Tip interactions with Lck and p80 result in downregulation of T cell receptor (TCR) and CD4 surface expression. Remarkably, these actions of Tip are functionally and genetically separable: the N-terminal p80 interaction is responsible for TCR downregulation and the C-terminal Lck interaction is responsible for CD4 downregulation. Thus, lymphotropic herpesvirus has evolved an elaborate mechanism to deregulate lymphocyte receptor expression to disarm host immune control.