Interference of the Epstein-Barr viral protein BNLF2a with the intracellular antigen transporter machinery TAP

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The *transporter associated with antigen processing* (TAP) is a pivotal element in the intracellular antigen processing pathway by being responsible for transport of antigenic peptides from the cytosol into the ER-lumen. Subsequently, translocated peptides are loaded onto major histocompatibility complex class I (MHC I) molecules via the peptide-loading complex (PLC) and are presented at the cell surface to cytotoxic T-lymphocytes. Herpesviruses have evolved strategies to escape this immune surveillance. During the lytic phase of Epstein-Barr virus (human herpes virus 4, HHV-4) infection, the viral protein BNLF2a interferes with antigen processing by preventing peptide loading of MHC I molecules. We demonstrate that BNLF2a is a tail-anchored protein, which is post-translationally inserted into the ER membrane, where it binds directly to the ABC-transporter TAP. Insertion of BNLF2a does not require TAP or any other component of PLC. The interaction sites of BNLF2a were mapped to the core TAP complex. BNLF2a arrests TAP in a transport-incompetent conformation, which excludes binding of the human cytomegalo viral TAP-inhibitor US6. Hence, the inhibition mechanism of Epstein-Barr virus protein BNLF2a is distinct and mutually exclusive of other viral TAP inhibitors.