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MHC Class I Molecules as a Target for Viral Immune Evasion

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Human cytomegalovirus (HCMV) is ubiquitous in human populations worldwide and has evolved intricate mechanisms for host immune evasion whereby latent or persistent viral infections follow primary infections. HCMV encodes at least four proteins that inhibit MHC class I antigen presentation and these proteins play an important role in allowing the virus to evade detection by CTL. HCMV US3 protein binds to and arrests MHC class I molecules in the endoplasmic reticulum. However, substantial amounts of class I molecules still escape US3-mediated ER retention, suggesting that not all class I alleles are affected equally by US3. We identify tapasin inhibition as the mechanism of MHC retention by US3. US3 directly binds tapasin, the key component of the peptide-loading complexes, and inhibits tapasin-dependent peptide loading, thereby preventing the optimization of the peptide repertoire presented by class I molecules. Due to the allelic specificity of tapasin towards class I molecules, US3 affects only class I alleles that are dependent on tapasin for peptide loading and surface expression. Accordingly, tapasin-independent class I alleles selectively escape to the cell surface. We will also discuss our findings on some of the diverse array of mechanisms employed by HCMV to inhibit the MHC class I pathway in order to escape CTL lysis. Investigation of these evasion strategies will not only improve our understanding of HCMV pathogenesis, but also provide unexpected, novel insights into basic cell biological and immunological processes.

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