Mature proteins derived from Epstein-Barr virus fail to feed into the MHC class I antigenic pool.

Abstract:

The immediate presentation of peptide epitopes on MHC class I (MHC I) after antigen expression has led to the concept that MHC I ligands are mostly derived from defective ribosomal products (DRiPs), a subset of newly synthesized proteins that are rapidly degraded by the proteasome. Whether and to what extent mature proteins contribute to the antigenic pool, however, has remained elusive. Here, we developed a conditional antigen expression system that allows studying antigen presentation from mature proteins by inducing their rapid proteasomal degradation in the absence of further antigen synthesis. Target cells in which expression of two Epstein-Barr virus (EBV) antigens was induced were rapidly recognized by antigen-specific CD8(+) T cells in a time- and dosage-dependent manner, demonstrating that antigen presentation was linked to antigen synthesis. By contrast, T cells failed to recognize target cells containing large amounts of mature protein even after induction of their rapid proteasomal degradation. Thus, the presentation of these antigens proved to be strictly dependent on protein synthesis whereas mature proteins failed to furnish the antigenic pool. These results have implications for the design of immunotherapeutic strategies that aim at targeting proteins with increased half-lives and are hence overexpressed in tumors.