Specific role for cathepsin S in the generation of antigenic peptides in vivo

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To address the role of different proteases in degradation of antigen destined for MHC class II-restricted presentation, we generated cathepsin-deficient mice carrying a transgenic B cell receptor (BCR) specific for hen egg lysozyme (HEL). We demonstrate that degradation of HEL in B lymphocytes is highly processive and does not result in discrete processing intermediates. Moreover, degradation of HEL does not require initial unlocking of the antigen by any of the cathepsins tested. Using mass spectrometry and microsequencing, we show that all major cathepsins (CatS, CatL, CatB, and CatD) digest HEL in vitro with considerable redundancy, although some preferential cleavages are evident. These observations have a functional correlate: when triggered by cathepsin S-deficient antigen-presenting cells, T cells that recognize different HEL epitopes fail to present two HEL-derived epitopes, while a third epitope is presented independently of the activity of cysteine proteases. We conclude that the proteolytic processing machinery is redundant, and that several proteases can substitute for each other to degrade a given antigen. However, a certain degree of proteolytic specificity is demonstrable for the generation of particular epitopes, notably by CatS.