Cathepsin G, and not the asparagine-specific endoprotease, controls the processing of myelin basic protein in lysosomes from human B lymphocytes

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The asparagine-specific endoprotease (AEP) controls lysosomal processing of the potential autoantigen myelin basic protein (MBP) by human B lymphoblastoid cells, a feature implicated in the immunopathogenesis of multiple sclerosis. In this study, we demonstrate that freshly isolated human B lymphocytes lack significant AEP activity and that cleavage by AEP is dispensable for proteolytic processing of MBP in this type of cell. Instead, cathepsin (Cat) G, a serine protease that is not endogenously synthesized by B lymphocytes, is internalized from the plasma membrane and present in lysosomes from human B cells where it represents a major functional constituent of the proteolytic machinery. CatG initialized and dominated the destruction of intact MBP by B cell-derived lysosomal extracts, degrading the immunodominant MBP epitope and eliminating both its binding to MHC class II and a MBP-specific T cell response. Degradation of intact MBP by CatG was not restricted to a lysosomal environment, but was also performed by soluble CatG. Thus, the abundant protease CatG might participate in eliminating the immunodominant determinant of MBP. Internalization of exogenous CatG represents a novel mechanism of professional APC to acquire functionally dominant proteolytic activity that complements the panel of endogenous lysosomal enzymes.