Specificity of human cathepsin S determined by processing of peptide substrates and MHC class II-associated invariant chain

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Cathepsin S (CatS) is a lysosomal cysteine protease of the papain family, the members of which possess relatively broad substrate specificities. It has distinct roles in major histocompatibility complex (MHC) class II-associated peptide loading and in antigen processing in both the MHC class I and class II pathways. It may therefore represent a target for interference with antigen presentation, which could be of value in the therapy of (auto)immune diseases.

To obtain more detailed information on the specificity of CatS, we mapped its cleavage site preferences at subsites S3-S1' by in vitro processing of a peptide library. Only five amino acid residues at the substrate's P2 position allowed for cleavage by CatS under time-limited conditions. Preferences for groups of amino acid residues were also observed at positions P3, P1 and P1'. Based on these results, we developed highly CatS-sensitive peptides. After processing of MHC class II-associated invariant chain (Ii), a natural protein substrate of CatS, we identified CatS cleavage sites in Ii of which a majority matched the amino acid residue preference data obtained with peptides. These observed cleavage sites in Ii might be of relevance for its in vivo processing by CatS.

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