

A2 Papain-like lysosomal cysteine proteases and their inhibitors: drug discovery targets?

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The physiological roles of papain-like lysosomal cysteine proteases now emerging from research are bringing them increasingly into focus as drug targets. These proteases are processive and digestive enzymes expressed in organisms from bacteria to humans. They have rather short active site clefts, comprising three well defined substrate binding subsites (S2, S1 and S1') and additional broad binding areas (S4, S3, S2', S3'). The geometry of the active site distinguishes them from other protease classes, such as serine and aspartic proteases, with six and eight substrate binding sites, respectively. Exopeptidases (cathepsins B, C, H, X), in contrast to endopeptidases (such as cathepsins L, S, V and F), possess structural features that facilitate binding of N- and C- terminal groups of substrates in the active site cleft. Besides a clear preference for free chain termini in the case of exopeptidases, the substrate binding sites exhibit no strict specificities. Instead, their subsite preferences arises more from specific exclusions of a substrate type. This presents a challenge for the design of inhibitors to target a specific cathepsin: only the cumulative effect of an assembly of inhibitor fragments can bring the desired result.