

## **A15** Cystatins

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Chicken egg white cystatin was characterised in the early 80s. Since then, the knowledge of a superfamily of similar proteins present in mammals, birds, fish, insects, plants and some protozoa has expanded and their properties as potent peptidase inhibitors have been firmly established. Today, 11 functional chicken cystatin relatives are known in man. The type 1 cystatins (A and B) are mainly intracellular, type 2 cystatins (C, D, E, F, G, S, SN and SA) extracellular and type 3 cystatins (L- and H-kininogen) intravascular proteins. All cystatins inhibit cysteine peptidases of the papain (C1) family and some also inhibit legumain (C13) family enzymes. Such proteases play key roles in the intracellular protein degradation (cathepsins B, H, L), are pivotal in the remodelling of bone (cathepsin K) and may be instrumental in controlling antigen presentation (cathepsin S, mammalian legumain).

The 3D structures of two of the human cystatins, cystatin C and D, have recently been determined. These structures together with results from mutagenesis studies shed light on 1) The C1 peptidase binding site, explaining the inhibitory specificities of cystatins; 2) The location and nature of the C13 peptidase binding site; and 3) The mechanism behind the syndrome Hereditary Cystatin C Amyloid Angiopathy, which results when a mutation in the cystatin C gene causes production of L68Q-cystatin C and leads to amyloidosis and brain haemorrhage in young adults.