

## LOW RESOLUTION STRUCTURE IN SOLUTION OF NATIVE HUMAN CYSTATIN C

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Human cystatin C (HCC) protein is a member of the family of the cysteine proteases inhibitors which inhibits proteins belonging to the papain and legumain families. HCC gen is located on chromosome 20 and codes a 120 amino acid protein. The general fold of monomeric form of cystatin has been defined by the crystal structure of chicken cystatin. Crystallographic studies of native HCC have shown that the protein exists in crystal in the form of symmetric three-dimensional domain-swapped dimers [1]. Dimerized human cystatin C has different overall conformation in tetragonal [2] and cubic [1] crystal forms. In tetragonal form (pdb: 1TIJ) HCC dimers present more elongated conformation than in cubic form (pdb:1G96).

This protein is also strictly related to the occurrence of one of the so-called conformational disease - the amyloidosis of the Iceland type. Mutational substitution of leucine to glutamine on position 68 causes protein oligomerization and deposition of amyloid fibrils.

Insoluble amyloid fibrils are found as deposits in patients with a range of diseases, *e.g.* Alzheimer disease, Parkinson disease, reactive amyloidosis, cystatin C amyloidosis, and the prionoses [3-5]. Knowledge of the molecular mechanism causing the transition of physiologically normal and soluble proteins to toxic oligomers and insoluble fibrils is essential for the development of treatment strategies for this group of common, but currently incurable, diseases.

SAXS measurements were performed on the X-33 EMBL beamline at DESY, Hamburg (Germany) using the Pilatus photon counting detector. Protein samples (2.9, 5.8 mg/ml) were measured in 50mM phosphate pH 6.7 buffer using synchrotron radiation (wavelength  $\lambda = 0.15$  nm) at temperature 283 K. The sample-to-detector distance was 1.7 m, corresponding to the scattering vector range from 0.06 to 5.2 nm<sup>-1</sup> ( $s = 4\pi \sin\theta/\lambda$  where  $2\theta$  is the scattering angle).

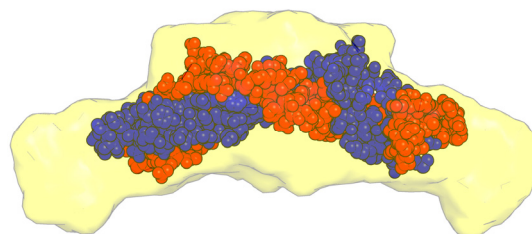


Figure 1. The low resolution model of human cystatin C in solution.

In this study we perform a small angle scattering experiment to probe the conformation and low resolution structure of HCC in solution. Using *ab initio* program DAMMIN we created low resolution 3D model of cystatin C in solution (Fig. 1). HCC form a dimer in solution with elongated conformation as in tetragonal crystal form.

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