Small angle X-ray scattering studies concerning the oligomerization of human cystatin C.

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Human cystatin C (HCC) is a small (13.3 kDa), soluble, basic protein, which has been identified in all bodily fluids including blood, urine, saliva, cerebrospinal as well as pleural fluids. The main role attributed to this protein is the inhibition of cysteine proteases belonging to the papain and legumain family, however, this protein also appears in some aspect of neurodegenerative disorders related to brain tumours, strokes, certain forms of epilepsy, Alzheimer's disease, and neurological autoimmune diseases[1]. In the physiological conditions, HCC molecule is a monomer but in pathological conditions it can form oligomers and amyloid fibrils. This kind of deposits were found in patients with spontaneous cerebral amyloid angiopathy[2] and hereditary cerebral amyloidosis - disease caused by point mutation changing leucine at position 68 to glutamate in HCC protein, what greatly accelerates the fibrils formation[3,4]. It is proposed that fibril formation process follows the "domain swapping" mechanism in which the N-terminal β1-α-β2 and C-terminal β2-AS-β4-L2-β5 fragments exchanges between two HCC monomers[5], but the exact mechanism is still elusive. Due to the increasing number of reported neurodegenerative diseases, undoubtedly related to the extended life expectancy, determination of HCC oligomerization conditions as well as its favourable factors invariably remains of great interest.

In this study, we analysed the low resolution structure and size of HCC using the combination of small angle X-ray scattering (SAXS) and dynamic light scattering (DLS) in solutions imitating various bodily fluids and potential oligomerization buffers. We have shown that low pH affects the monomer-dimer equilibrium promoting dimer formation. We were also able to isolate and characterize the tetrameric form of HCC at low pH. In addition we analysed the structure of HCC amyloid fibrils formed under studied conditions by atomic force microscopy (AFM).

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