SOLUTION SCATTERING STUDIES OF HUMAN CYSTATIN C MUTANTS

M. Taube [1], Z. Pietralik [1], A. Szymańska [2], and M. Kozak [1*]

[1] Departament of Macromolecular Physics, Faculty of Physics, A. Mickiewicz University, Umultowska 85, 61-614 Poznań, Poland

[2] Department of Medicinal Chemistry, Faculty of Chemistry, University of Gdańsk, Sobieskiego 18, 80-952 Gdańsk

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**) e-mail: mkozak@amu.edu.pl*

Human cystatin C (HCC) is a cysteine protease inhibitor which, in pathological conditions, undergoes dimerization *via* domain swapping. HCC point mutation Leu68Gln is responsible for occurring of hereditary amyloid angiopathy. The symptoms of this disease includes cerebral hemorrhage, stroke, and dementia as a result of amyloid deposition within arteries in the brain [1].

On the molecular level the crucial step in amyloid formation is dimerization of cystatin C. In this process the monomeric cystatin C molecule partially unfolds and, after exchanging of N-terminal domains, forms a dimer with another cystatin molecule. As a result, new β-sheet structure, consisting of residues Ile56 -Gly59 corresponding to loop L1 in the monomeric molecule is formed between two distinct chains.

Unwinding of L1 is the most pronounced structural change in HCC structure occurring as a result of dimerization because swapped domains reconstitute monomer structure. Circular dichroism and molecular dynamics studies indicate that valine exchange for proline may destabilize the structure of L1 loop while asparagine and aspartic acid my favor more stable conformation [2].

In this study we have performed a small angle scattering experiments on HCC mutants Val57Pro, Val57Asn, Val57Asp to probe the effect of these mutations on cystatin C structure in solution. SAXS measurements were preformed on the X-33 EMBL beamline at DESY, Hamburg (Germany) using the Pilatus photon counting detector [3]. On the basis of scattering curve we have determined low resolution structures of Val57Asn and Val57Asp using *ab-initio* modeling software DAMMIN [4].

Val57Pro mutant in solution rapidly forms oligomers in contrast to two other mutants. Val57Asn and Val57Asp have elongated conformation similar to the wild type dimers and undergo slow oligomerization.

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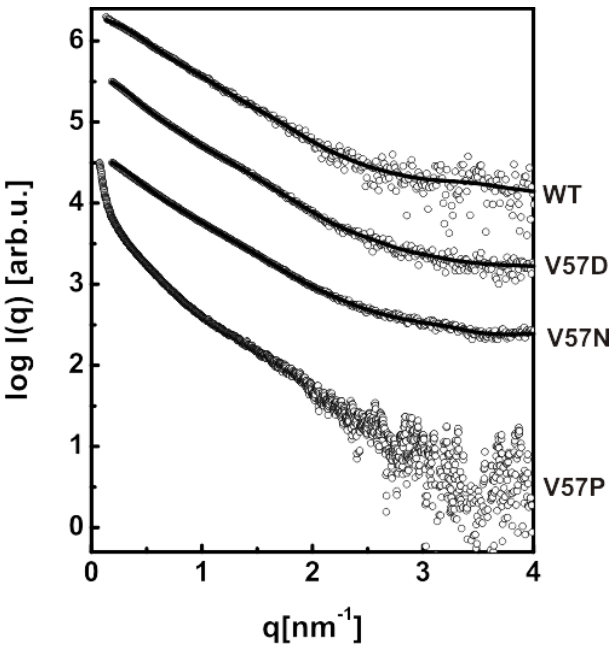

Figure 1. Small angle X-Ray scattering curves (black circles) recorded for wild type (WT) and various Val57 mutants together with fit from models generated by *ab initio* modeling program DAMMIN (black lines).