ATOMISTIC SIMULATIONS OF PAP248-286 PEPTIDE OLIGOMERIZATION

Nikitina A., Yulmetov A., Kusova A.[1], Klochkov V., Blokhin D.

Kazan Federal University, Kremlevskaya Str., 18, Kazan, 420008, Russian Federation, +7(843)2337012, annanikitina199737@gmail.com
[1]Kazan Institute of Biochemistry and Biophysics, FRC Kazan Scientific Center, Russian Academy of Sciences, Lobachevsky 2/31, Kazan, 420111, Russian Federation

Amyloid fibrils are ordered aggregates that from a wide variety of soluble proteins and peptides. Amyloid fibrils take part into more than 20 human diseases, including Alzheimer's, Parkinson, Huntington and HIV infection. The association of certain proteins with the fibril structure formation characterizes the pathological manifestation of amyloid diseases. Clarification of the physicochemical parameters of the amyloid fibril formation is critical to our understanding and subsequent treatment of amyloid diseases. There are several comprehensive studies of self-assembly mechanisms of functional and pathogenic polypeptides.

Semen is the major vehicle for the spread of the HIV infection. Accumulating evidence shows that semen boosts HIV infection. An amyloid fibrils SEVI (semen-derived enhancer of virus infection) contribute to the HIV enhancing effect of semen. SEVI forms from peptide fragments of prostatic acid phosphatase (PAP): PAP248-286 and PAP85-120. SEVI captures viral particles and promotes their attachment to target cells and subsequent intensification of viral fusion and infection. Study of the initial fibrillation stage, i.e., polypeptide homooligomerization is necessary to understand interaction between the SEVI, virion and cells. Oligomers of polypeptides are often short-lived and not available for most experimental techniques. Molecular modeling is a powerful and unique tool for observation these complex objects. We used an advanced accelerated sampling method metadynamics to characterize the oligomerization landscape of the amyloidogenic peptide PAP248-286. The amyloidogenic peptide PAP248-286 oligomers (dimer, trimer, tetramer, hexamer, heptamer) structures were obtained. Based on the molecular dynamics data we have shown that PAP248-286 molecules have a horseshoe shape with bends in the regions of amino acid residues A274 and N269 in the dimeric state. The horseshoe shape of PAP248-286 backbone chain is consistent with the model of steric zipper that has been proposed for the mechanism of amyloid fibril formation. The increase in the length of the helical regions and their parallel arrangement caused by the oligomerization process was observed consistent with the mechanism of amyloid formation. It was confirmed that the process of fibril formation of an amyloidogenic peptide PAP248-286 begins with a pairwise parallel arrangement of the helical regions of the polypeptide molecules. The data obtained can be used for the developing an approach of point mutations design that affects the PAP248-286 fibrillation process.

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