Tetramer of Chimeric Aβ-IgNARs as a Model for Amyloid-β Oligomer Formation in Alzheimer's Disease

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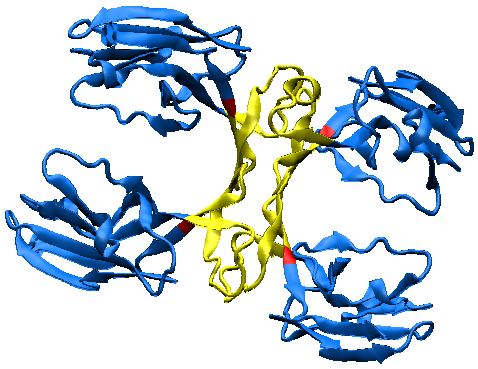
Alzheimer's disease (AD) is the most common neurodegenerative disorder: an estimated 30 million people worldwide are affected with AD.[1] AD can be diagnosed post mortem for instance by the increased presence of amyloid plaques in the brain. Due to the fact that amyloid plaques are extracellular deposits, which are primarily composed of insoluble Aβ fibrils, it is widely believed that amyloid-β peptides (Aβ) have a causal role in AD.

In recent studies, the small Aβ oligomers were in the centre of interest because they showed a higher cytotoxicity than insoluble Aβ fibrils.[2] However, structural information on these Aβ species is restricted, because of their noncrystalline and unstable nature. Recently, Streltsov et al. described a crystal structure of the amyloidogenic residues 18-41 of the Aβ peptide genetically engineered into the CDR3 loop region of a shark Ig new antigen receptor (IgNAR) single variable domain antibody.[3] The chimeric proteins build a homo-tetramer as a quaternary structure through interactions mediated by the inserted Aβ peptide component and the authors suggested this tetrameric structure as a potential model system for nonfibrillar oligomer formation in AD.[3]



The objective of our study is to investigate the stability and dynamics in solution of the crystallised chimeric structure (PDB ID code 3MOQ) and the inserted amyloid-β p3 fragment by means of molecular dynamics simulations.

For our investigations, we not only examined the tetrameric structure itself, we also split the structure into different dimers and all possible monomers. Our first results show a stable dynamical behaviour of the structures in explicit solvent and no changes of the protein fold. Furthermore, we observed that every single subunit of the tetrameric structure is conformationally more stable than the whole dimer or tetramer, because the individual subunits exhibit large hinge motions with respect to each other. Additionally, we noticed the highest structural flexibility in the region of the Aβ peptide component and found some crystal packing effects of the published structure.

[1] D. M. Holtzman, J. C. Morris, A. M. Goate, *Sci Transl Med*, **2011**, *3*, 77sr1.
[2] V. H. Finder, R. Glockshuber, *Neurodegenerative Dis*, **2007**, *4*, 13-27.
[3] V. Streltsov, J. Varghese, C. Masters, S. Nuttall, *J Neurosci*, **2011**, *31*, 1419-1426.