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The Ligand Binding to the Gamma-Secretase Complex

Jakub Jakowiecki*, Urszula Orzeł, Krzysztof Młynarczyk and **Sławomir Filipek**
Faculty of Chemistry, University of Warsaw, Poland

Alzheimer's disease is the most common progressive neuro degenerative disorder and is characterized by the presence of amyloid β (Aβ) plaques and neurofibrillary tangles in the brain. No treatments are yet available to cure Alzheimer's disease however, soluble Aβ oligomers are believed to play a crucial role in the neuro inflammation that is observed in this disease. The γ-secretase complex, which produces a β, consists of the catalytic subunit presenilin which is associated in a 1:1:1:1 stoichiometry with three subunits: PEN-2, APH-1 and nicastrin (NCT). Recently, the cryo-electron microscopy (cryo-EM) structures of the apo form of this complex [1], as well as with an inhibitor [2], were obtained. The γsecretase is an intramembrane-cleaving protease involved in Alzheimer's disease, cancer and other disorders. The clinical trials with the γ-secretase inhibitors have however, demonstrated that unselective inhibition of γ-secretase causes serious toxicity. Evolving insights suggest that more subtle modulations of γ-secretase proteolysis are potentially valuable approaches.

Using the refined 3.4 Å cryo-EM structure of γ-secretase we investigated unfolding and binding of substrate C99 (C-terminal fragment of amyloid precursor protein) as well as inhibitors to the membranous part of γ-secretase exploring primary and secondary binding sites. We also uncovered conformational dynamics of C99 and inhibitors which can have a great influence on mechanism of substrate cleavage by this enzymatic complex.

Biography:

Jakub Jakowiecki graduated from a high school with natural profile. Afterwards he studied at the Interfaculty Individual Studies in Mathematics and Natural Sciences (MISMaP) at University of Warsaw. In 2008 he received his Masters degree in Chemistry (specialization: organic chemistry) and started his PhD studies in organic chemistry at University of Missouri (Columbia, Missouri in United States) which he has not finished because of health problems. In 2013 Jakub changed his specialization to theoretical chemistry and started a PhD research in biomodeling group directed by prof. Sławomir Filipek at the University of Warsaw. He has been studying G-Protein Coupled Receptors (GPCRs) and other membrane proteins ever since. His scientific interests focus on GPCRs binding hydrophobic ligands, especially cannabinoid and sphingosine1phopshate receptors, which are the topic of his PhD thesis. He also works in the project which aims to find a cure for Alzheimer's disease and participates in a development of GPCRM modeling service (a non-profit web service for GPCRs modeling). In his research Jakub uses techniques such as: Homology modeling, *ab initio* modeling, docking, interaction fingerprints (IFPs) and molecular dynamics simulations (MD) plus various modifications of this method such as steered molecular dynamics (SMD), supervised molecular dynamics (SuMD) and replica exchange molecular dynamics (REMD).