Mirza et al. BMC Genomics 2014, 15(Suppl 2):P10
http://www.biomedcentral.com/1471-2164/15/S2/P10

BMC Genomics

POSTER PRESENTATION Open Access

Crystallography based structure elucidation of the complex of C-terminal fragment of Aβ polypeptide of Alzheimer's disease with phospholipase A_2

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From 2nd International Genomic Medical Conference (IGMC 2013)
Jeddah, Kingdom of Saudi Arabia. 24-27 November 2013

Background

Aggregation of Aβ polypeptide plays an important role in pathogenesis of Alzheimer's disease, the most common form of dementia [1]. Therapies based on rationally designed aggregation inhibitors require knowledge of molecular structure [2]; because of high aggregation tendency of Aβ, it has not been possible to obtain complete structural information by X-ray crystallography. The hydrophobic C-terminal part of the Aβ peptide is critical in triggering transformation from α-helical to β-sheet structure. Phospholipases are an important enzyme involved in the inflammatory cascade mechanism having a conserved globular structure with active site, calcium binding loop, and hydrophobic channel. It has been speculated that phospholipase A_2 (PLA_2) inhibits the aggregation of Aβ peptide by interacting with the peptide and keeping the two peptide chains apart.

Material and methods

PLA_2 was purified to homogeneity from cobra venom. In order to examine the nature of interactions between PLA_2 and $Aβ_{36-42}$ peptide 1:1 complex of PLA_2 with the C-terminal heptapeptide Val-Gly-Gly-Val-Val-Ile-Ala was prepared and co-crystallized. It is in tetragonal space group $P4_1$ with unit cell dimensions, a=b=42.6 Å, c=65.8Å. X-ray intensity data were collected to 2.04 Å resolution. Structure has been determined by molecular replacement and refined to the crystallographic R factor of 0.193. Structural co-ordinates were deposited at RCSB's PDB (3GCI).

Results

Peptide binds to PLA_2 at the hydrophobic substrate binding site and forms at least eight hydrogen bonds and about a two dozen Van der Waals interactions indicating that the affinity between PLA_2 and the heptapeptide is far greater than the affinity between two Aβ peptide chains. Therefore, PLA_2 may have a potential role to prevent the aggregation of Aβ peptides. Calcium has been found in the calcium binding site and has pentagonal bipyramidal geometry. Kinetic studies showed that the peptide VGGVVIA binds to PLA_2 in a competitive manner with a binding constant of 5.2×10^{-7} M.

Conclusions

This is the first attempt to structurally establish the interaction between Aβ peptide and PLA_2. Results indicate that the peptide mainly adopts β-sheet secondary structure. Understanding the mechanism and effects of PLA_2 upregulation in AD brain may help in the development of novel strategies to inhibit the inflammatory responses and delay AD progression. Preventing the folding of nascent Aβ monomer into toxic conformers or oligomers would have therapeutic benefits.

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Published: 2 April 2014

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doi:10.1186/1471-2164-15-S2-P10
Cite this article as: Mirza *et al.*: Crystallography based structure elucidation of the complex of C-terminal fragment of Aβ polypeptide of Alzheimer's disease with phospholipase A_2. *BMC Genomics* 2014 **15**(Suppl 2):P10.