MEETING: International Alzheimer's & Parkinson's Diseases Congress - AD/PD™, Florence March 2013

Mutation of a GxxxA motif in amyloid-beta peptide sequence strongly impairs its oligomerization in cells.

Decock M.[1], Marinangeli C.[1], Stancu IC. [1], **Stanga S.**[1], Dewachter I.[1], Octave JN.[1], Constantinescu S.N.[2], Kienlen-Campard P.[1]

[1]Alzheimer Research Group, Institute of Neuroscience, Université catholique de Louvain, B-1200 Brussels (Belgium). [2]Cell Signalling Group, Christian de Duve Institute and Ludwig Institute for Cancer Research, Université catholique de Louvain, B-1200 Brussels (Belgium).

Objectives

Recent data indicate that the oligomeric forms of Aβ induce neurodegeneration and loss of neuronal functions. Oligomers ranging from dimers to dodecamers have been described, but our understanding of the mechanisms leading to the formation of these toxic oligomers is scarce. The Aβ sequence possesses particular GxxxG and GxxxG-like motifs (GxxxA) that have been reported to promote self-association of transmembrane proteins. The aim of the project is to study the contribution of these motifs to Aβ oligomerization.

Methods

The GxxxG and GxxxA motifs of Aβ sequence were mutated to LxxxL in vectors expressing either directly Aβ 42 or the amyloidogenic C-terminal fragment of APP (C99). These constructs were expressed in CHO cells. The formation of Aβ oligomers was analyzed by Western blotting and further confirmed by mass spectrometry. Adeno-Associated Viruses (AAVs) were produced in order to study Aβ oligomerization in neuronal cells and in vivo following viral injection.

Results

Our results showed a dramatic decrease in oligomerization for the GxxxA motif mutants. The mutation of Glycine 38 is sufficient to block Aβ oligomerization in cells. On the contrary, mutation of the GxxxG interface triggered the formation of more Aβ oligomers. We are currently extending these findings to neuronal cells and in vivo.

Conclusions

Our results first indicated that a significant part of Aβ produced in cells (CHO) is present as membrane oligomers. Mutagenesis studies allowed to identify Glycine 38 as a critical position for Aβ oligomerization in cells.