Research Highlights

Highlights from the latest articles in Alzheimer's disease

Amyloid fibrils, oligomers, dimers…

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Evaluation of: Jin M, Shepardson N, Yang T, Chen G, Walsh D, Selkoe DJ. Soluble amyloid β-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. *Proc. Natl Acad. Sci. USA* 108(14), 5819–5824 (2011).

Alzheimer's disease is characterized by the presence of two aberrant structures found in the brain of the patients: senile plaques (SPs) and neurofibrillary tangles. The main component of SPs is the β-amyloid peptide (Aβ) whereas the main component of neurofibrillary tangles is tau protein in its phosphorylated form. Genetic studies have suggested that in many cases of familial Alzheimer's disease, neurodegeneration is promoted by the appearance of Aβ that could play an initial role in the onset of the disease upon aggregation. For several years, Aβ aggregates have been proposed to be responsible for the toxic action of SPs. Next, Aβ protofibrils were suggested to be toxic, then oligomers and now, in this paper, it is indicated that Aβ dimers are sufficient to induce neurite degeneration. Moreover, it is suggested that this degeneration involves the disruption of the neuritic cytoskeleton, a feature that is dependent on the presence of tau protein. This role for tau confirms previous results from other laboratories.

There are two points in this study that require further comment. First, the authors claim that Aβ dimers are present and can be isolated from the brains of Alzheimer's disease patients. Second, there are several extracellular factors that act on surface receptors only in their dimeric form. Aβ aggregates have been found to interact with several cellular receptors. However, little is known about the affinity of every Aβ aggregate, from Aβ protofibrils to Aβ dimers, to all of these proposed receptors. In addition, it will be of interest to further investigate whether the signaling pathways promoted by Aβ dimers differ from the ones triggered by Aβ oligomers, and to address the putative role of tau protein in these pathways.

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A way to look at tangles *in vivo*

Evaluation of: Fodero-Tavoletti MT, Okamura N, Furumoto S *et al.* ^{18}F-THK523: a novel *in vivo* tau imaging ligand for Alzheimer's disease. *Brain* 134(Pt 4), 1089–1100 (2011).

Detection of the presence of the two main histopathological hallmarks in live Alzheimer's disease patients is an important task in the diagnosis of this neurodegenerative disorder. These two aberrant structures are senile plaques (SPs) and neurofibrillary tangles. SPs can be detected *in vivo* through the use of imaging radiotracers such as Pittsburgh Compound B (PiB). PiB is an imaging agent, related to Thioflavin T, which mainly binds to aggregated β-amyloid peptide (the main component of SPs), and only at very high concentrations binds to tau aggregates.

In 2005, a Japanese group [1] described which quinoline and benzimidazole derivates could be suitable imaging radiotracers to analyze tau pathology. In the work by Fodero-Tavoletti, a quinoline derivative, ^{18}F-THK523, is described as a good imaging radiotracer for tau aggregates. This compound shows two

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important features: it binds specifically to neurofibrillary tangles with no detectable binding to SPs, and it has the adequate lipophilicity to cross the blood–brain barrier. On the other hand, interaction of the compound with tau aggregates is in the low nanomolar range.

A point that remains to be addressed is the molecular mechanism by which ^{18}F-THK523 specifically binds to tau aggregates. In the case of PiB interaction with β-amyloid peptide, the compound has been suggested to bind, like thioflavin, to proteins with a high content of β-sheet structure. Elucidating whether ^{18}F-THK523 binds to proteins with a specific secondary structure or if its binding specificity is due to other features needs further investigation.

Reference

1 Okamura N, Suemoto T, Furumoto S *et al.* Quinoline and benzimidazole derivatives: candidate probes for *in vivo* imaging of tau pathology in Alzheimer's disease. *J. Neurosci.* 25(47), 10857–10862 (2005).

Amyloid could not be enough

Evaluation of: Robakis NK. Mechanisms of AD neurodegeneration may be independent of Aβ and its derivatives. *Neurobiol. Aging* 32(3), 372–379 (2011).

An important role for the β-amyloid (Aβ) peptide in the onset of Alzheimer's disease (AD) has been postulated [1]. In the neurodegeneration field it is difficult to affirm that a single molecule, like Aβ, could be the only one responsible for the promotion of a disease. However, it is nowadays a kind of established dogma that Aβ is the cause of AD. Nevertheless, a number of long-lasting dogmas in science have proven to be wrong and have been replaced by other theories, considered heretic in principle. For instance, Cajal, a pioneer for his time, presented the novel and heretic neuron theory in contradiction with the accepted reticular theory, thereby establishing the basis for modern neuroscience. In addition, research by Dr Manuelidis has put into question the widely accepted dogma that the infectious agent of mad cow disease is the prion protein, arguing in favor of a virus-triggered disease [2].

In line with this, Robakis argues against the established dogma, suggesting that only the presence of Aβ aggregates is not sufficient to explain the onset of all cases of AD. In this work, the author suggests that in familial AD, mutations in the *PS1* gene could result in a gain or loss of function of PS-1. Gain of function of the PS1 protein will result in an increase in Aβ peptide levels. On the other hand, it has been found that some *PS1* mutations fail to increase production of Aβ peptide but can result in the onset of dementia. Thus, there are some mutations related to AD whose effects on neurodegeneration may be independent of their effects on Aβ production. Therefore, we should be aware that in addition to those cases where an increase in the amount of Aβ is the first step for the initiation of the disease, there are other cases in which the mechanisms responsible for the degeneration are poorly understood. Taking together all AD cases, it might be useful to focus not only on the first step in the onset of the disease, but also downstream, to look for points of convergence that could be used as suitable targets for future therapies. One of these convergent points under intense investigation is GSK3, given its wide involvement in amyloid toxicity, effect of presenilin mutations, and tau phosphorylation in AD.

References

1 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297(5580), 353–356 (2002).

2 Couzin-Frankel J. Scientific community. The prion heretic. *Science* 332(6033), 1024–1027 (2011).