Interaction of BIN1 and Tau: physiological functions and pathological consequences in Alzheimer’s disease.

https://neurodegenerationresearch.eu/survey/interaction-of-bin1-and-tau-physiological-functions-and-pathological-consequences-in-alzheimer%c2%92s-disease/

Principal Investigators

LAMBERT Jean-Charles

Institution

Institut Pasteur de Lille

Contact information of lead PI
Country

France

Title of project or programme

Interaction of BIN1 and Tau: physiological functions and pathological consequences in Alzheimer’s disease.

Source of funding information

ANR

Total sum awarded (Euro)

€ 585,936

Start date of award

01/11/2015

Total duration of award in years

4.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Alzheimer’s disease (AD) is the leading cause of dementia. The main pathological features of AD are neurofibrillary tangles and senile plaque formation. The latter is caused by the

progressive deposition of amyloid ß protein (Aß) in the brain.
There is no longer any doubt that a strong genetic predisposition to AD exists (accounting for 60% to 80% of the attributable risk). To characterize genetic components in AD, we and others have developed systematic, high-throughput genomic approaches (as part of genome-wide association studies, GWASs) and recently reported the characterization of 21 common genetic determinants of AD, including the bridging integrator 1 gene (BIN1). This gene currently ranks second after APOE in the AlzGene database of published meta-analyzed AD risk loci. However, the genetic and molecular mechanisms by which BIN1 affects the AD risk are not known.
We recently studied the molecular mechanism by which BIN1 protein might modulate the disease process in AD. Taken as a whole, our data suggest that BIN1 AD risk variants are associated with BIN1 expression and modulate AD pathogenesis through Tau rather than through an amyloid pathway. We have also identified genetic, neuropathologic and biochemical interactions between Tau and BIN1 in vitro and in vivo. Furthermore, we have performed a detailed characterization of the BIN1 and Tau protein interaction domains (unpublished data). In conclusion, we have potentially identified the first genetic risk factor for AD linked to tauopathy (Chapuis et al, Mol Psychiatry, 2013).

Our results raise important new questions about BIN1's involvement in the AD process:
(i) How are these interactions controlled?
(ii) What are the physiological and disease-state consequences of these interactions?
(iii) Which partners modulate these interactions and thus may be involved in the AD process?
(iv) How do BIN1 over-expression and its interaction with Tau modify the development of the AD process?

In order to address these relevant questions, we intend to evaluate BIN1's involvement in the AD process by:
(i) Characterizing potential modulators of the BIN1-Tau interaction, i.e. specific phosphorylation status of Tau or BIN1.
(ii) Characterizing the physiological and physiopathological implications of the Tau-BIN1 interaction with regard to A? peptide or glutamate exposure.
(iii) Determining BIN1 partners that are likely to modulate both the normal and harmful consequences of the Tau-BIN1 interaction (through the combined use of proteomics, high-content screening and Drosophila models).
(iv) Developing and studying transgenic mouse models that conditionally under- or over-express BIN1 in neurons and develop (or do not develop) AD lesions, e.g. tauopathy.

By probing BIN1's involvement in AD, this multidisciplinary project will improve our understanding of the AD process and should enable us to determine whether BIN1 and its cellular pathways are potential drug targets.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
France

Diseases:

Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A