Spreading of Tau assemblies

https://neurodegenerationresearch.eu/survey/spreading-of-tau-assemblies/

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Country

France

Title of project or programme

Spreading of Tau assemblies

Source of funding information

ANR

Total sum awarded (Euro)

€ 587,746

Start date of award

01/10/2014

Total duration of award in years

4.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias|Neurodegenerative disease in general

Keywords
Research Abstract

The study of the brain diseases with protein aggregates also called proteinopathies as Prion disorders, Parkinson’s disease or Alzheimer’s disease has opened new questioning. In fact, aggregation of proteins related to these diseases (PrP, alpha-synuclein, amyloid peptide and Tau) is tightly associated to neuronal death. Such protein aggregates would have biochemical and infectious prion-like characteristics allowing them to imprint their intrinsic structure onto the normal forms of their constituting proteins and act by trans-cellular transfer of the pathological property. Such transfer allows for pathology spreading, which is made according to precise

cellular pathways.
In the project SPREADTAU, we focus our interest on microtubule-associated Tau proteins. These proteins aggregate in numerous neurodegenerative disorders so-called Tauopathies of which the most known is Alzheimer’s disease. In the brain, there are six Tau isoforms having three (3R) or four microtubule-binding domains (4R). Whereas the six Tau isoforms (3R/4R) aggregate in the brain of Alzheimer’ patients, only 4R Tau isoforms form fibrils in other Tauopathies such as progressive supranuclear palsy. Conversely, in Pick’s disease, only 3R Tau isoforms aggregate suggesting the existence of an isoform-specific mechanism. Finally, hierarchical pathways of this neurodegeneration have been well established in Alzheimer’s disease and other sporadic tauopathies such as argyrophilic grain disorder and progressive supranuclear palsy but the molecular and cellular mechanisms supporting this progression are yet not known. Deciphering how and which toxic Tau species are implied in the trans-cellular transfer of Tau pathology will define new perspectives not only in diagnosis of neurodegenerative diseases but also in therapeutical development.
To address these fundamental questions, the consortium proposes, first of all, to study the nucleation and fibrillogenesis of the different Tau assemblies either individually or mixed in various environments: test tube, cell culture or rodent brain. Once characterized, Tau assemblies will be used to determine the cellular tropism (either in neurons or glial cells) of Tau isoforms/assemblies and to evaluate their efficiency to be transported in neurons between the soma-dendritic compartment and the axon. Their subsequent secretion in the extra-cellular medium and ability to be transferred from primary cell (donor cells) to secondary cell population (recipient cells) will be done using dedicated microfluidic devices. This will allow to the consortium for deciphering which Tau assemblies and which cell types in the brain are implied in the trans-cellular transfer of Tau. Such findings may help to the understanding of the progressive and hierarchical appearance of Tau pathology in sporadic tauopathies. Finally, we will test the hypothesis of prion-like Tauopathy by validating Tau capacity to pass on its misfolding to normal Tau proteins in keeping the notion of strains likely to be related to 3R and 4R characteristics. All of these questions will be addressed in vitro by using original and dedicated microfluidics systems and validated in vivo in the rodent brain

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
France

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Alzheimer's disease & other dementias, Neurodegenerative disease in general

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2016

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