

Présentation des projets financés au titre de l'édition 2010 du
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AD HOC

Cell therapy and Alzheimer's disease: therapeutic potential and mechanisms of action of human olfactory nasal stem cells

Abstract

At present, Alzheimer's disease (AD) affects 7 million European people. U.S. society spends at least \$100 billion a year on AD and it is expected that AD will cost \$500 billion a year by 2020. In addition to memory loss, AD is characterized by an extensive cell death. Worldwide, we are one of the three laboratories that have developed an efficient method for cultivating and purifying human nasal olfactory stem cells. We also demonstrated that these cells are multipotent and represent a potential source for autologous stem cell therapy in Parkinson's disease.

The three academic partners of the current application showed for the first time that human nasal olfactory stem cells, transplanted in a mouse model of amnesia, restore learning and memory. Noticeably, adult human OE-MSCs i) migrated towards cerebral lesioned areas, ii) differentiated into neurons, iii) restored long term potentiation (LTP) and iv) promoted recovery of mnemonic deficits. Interestingly, similar results were observed when OE-MSCs were injected into the cerebro-spinal fluid (CSF). In addition, we observed that intravenously transplanted OE-MSCs home in lesioned hippocampi. We now aim to confirm this therapeutic benefit in a transgenic mouse model for AD. In order to get closer to patients' bed, we will assess behavioural and electrophysiological recovery when olfactory stem cells are intravenously grafted.

AD HOC project involves three academic teams and a biotech company, VECT-HORUS, with a recognised expertise on the passage of the blood-brain barrier (BBB), that have already worked and published together. Using a transgenic AD mouse model (5xFAD) which displays cell loss and mnemonic deficits, we will compare poorly invasive routes for cell delivery, namely intra-CSF and intra-blood transplantations. More specifically, our aims are to:

- o assess the therapeutic benefit of an intravenous OE-MSC delivery
- o unveil the cellular and molecular mechanisms involved in OE-MSC transmigration across the BBB and migration through the brain parenchyma.
- o assess the role of amyloid beta peptides on the metabolism

of OE-MSCs

Expected results

All techniques are in hand and no major technical drawback should be experienced. If our experiments are successful, we expect to:

- o corroborate previous data on the beneficial repairing capacities of OE-MSCs and confirm that they can restore memory in an AD mouse model. We also wish to take a step forward in order to confirm that OE-MSCs can cross the BBB, home to lesioned areas and can be, in the future, transplanted in the blood;

- o gain a better knowledge of the basic mechanisms underlying targeting of therapeutic cells to lesioned zones of the CNS;

- o increase our knowledge on the molecular machinery used by OE-MSCs to cross the BBB and migrate through the brain parenchyma. We also anticipate to further disclose the signaling pathways involved in stem cell differentiation when in contact with amyloid beta peptides.

Since nasal OE-MSCs can be collected in every living individual, under local anaesthesia, and do not induce tumours, our work paves the way for clinical trials based on autologous transplantation, similarly to what we have done with another olfactory cell type in paraplegic patients.

Partners

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Michel VIGNES
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Coordinator

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ANR funding

580 000€

**Starting date
and duration**

March 2011 – 36 months

Reference

ANR-10-MALZ-005

Cluster label

EuroBioMed (ex ORPHEME)

APPNET

Netrin-1 as a ligand for APP receptor: molecular mechanism and implication in Alzheimer disease

Abstract

Despite the extensive research on Alzheimer's disease (AD) since its first description in 1907—including the sequencing of A β peptide in 1984 and cloning of its precursor, APP (β -amyloid precursor protein), in 1987—little is known about potential ligand interactions with APP, or about any associated ligand-dependent downstream signaling. During the course of the previous ANR "neuroscience", P. Mehlen's laboratory identified the guidance cue and trophic factor netrin-1 as a ligand for APP. They showed that this interaction affects APP signaling (including increased transcriptional activity of the APP intracellular domain (AICD)) and they showed that APP is required for netrin-1 function during growth of cortical neurons during development. Of great interest, netrin-1 binding to APP was then shown, both in vitro and in vivo to inhibit the generation of the A β peptide that is key in AD (Patent CNRS/The Buck Institute for Age Research, n° 00532-050).

The identification of netrin-1 as a potential ligand for APP raises many questions regarding the potential role(s) of netrin-dependent APP signal transduction in neuronal development and degeneration but it may have also crucial importance in term of putative therapeutic development. Indeed, it would be of great interest to develop a compound that mimics netrin-1 as a candidate drug against AD. In the current application, two complementary partners (cell biology and animal models versus protein structure) propose to examine some of the critical questions related to the importance of netrin-1 in APP function and to bring this observation closer to drug development. First as a basic question, we would like to assay whether APP behaves as netrin-1 dependence receptor, that is to say that netrin-1, by interacting with APP, inhibits the known pro-apoptotic activity of APP, an activity that we believe is associated, in combination with A β toxicity, with AD progression. Second we would like to demonstrate that netrin-1 controls not only Ab formation in AD mouse model but also the different hallmarks of the AD pathology. Third, we would like to determine the structure of the interaction APP/netrin-1 in order to define, using in silico screens and an high-through-put screen for small molecules, lead compounds that may mimic netrin-1 or that may increase netrin-1/APP interaction and as consequence may lead to an improvement of AD.

The project presented in this ANR "MALZ" call will first provide more basic knowledge to the relative importance of netrin-1 in APP function. It shall (i) describe the nature of the

interaction between netrin-1 and APP, (ii) precise whether netrin-1 not only affects A β formation but also formation of another toxic fragment called C31 generated after caspase cleavage of APP, and (iii) show whether netrin-1 level affects AD phenotype (and not only A β formation) in an AD mouse model. This basic knowledge shall then be used to predict, design or characterize lead compounds that may in turn inhibit/delay AD progression.

Partners Jean-Luc Ferrer

Coordinator Patrick MEHLEN

ANR funding 680 000€

Starting date and duration March 2011 - XX months

Reference ANR-10-MALZ-008

Cluster label

CoRehAlz

Cellular, molecular and systems-level mechanisms underlying the establishment of a brain cognitive reserve in a mouse model of Alzheimer's disease

Abstract

The "cognitive reserve" model suggests that individuals with greater brain reserve capacity (i.e. with higher level of education or occupational attainment) may develop resilience to neurodegenerative damage and optimize behavioral abilities through differential recruitment of neural networks and/or alternative cognitive strategies. Our preliminary data highlight the beneficial effects of exposure to environmental enrichment (EE) used as a rehabilitative therapy in rodents. Building upon these solid results, the goal of this 3.5 year project is to unravel some of the mechanisms by which EE: (1) reduces/delays the onset of memory deficits associated with Alzheimer's disease (AD) and (2) delays the occurrence of neuropathological brain markers such as amyloid deposits during the aging process.

We hypothesize that the beneficial effects of enrichment could rely on long-lasting and stable modifications of the cerebral networks involved in cognitive functions. The originality of our approach lies in administering EE early in life and for a time-restricted period to enable long-lasting cerebral modifications in the form of a "cognitive reserve". To mimic AD pathology, a well characterized transgenic mouse model of this disease will be used (i.e. Tg2576 transgenic mice exhibiting a slow time-related progression of the disease suitable to accommodate specific exposures to EE) to characterize the cellular and molecular mechanisms underlying the establishment of this cognitive reserve that could later in life make brain functions more resilient to the deleterious effects of AD. The proposed experiments, organized in the form of 8 interdependent tasks, will benefit from a consortium of 3 partners with a high level of complementary expertise in the fields of Cognitive Neuroscience and Vascular Physiology. Task 1 will be focusing on the production and genotyping of transgenic AD mice (Tg2576). Task 2 will characterize the kinetic of effects of EE on memory function in AD mice. Task 3 will map the dynamics of reorganization of hippocampal-cortical networks during spatial memory processing in AD mice exposed to EE. Using electrophysiological recordings, Task 4 will examine the effects of EE on synaptic plasticity in AD mice. Characterization of the EE-induced reorganization and reactivity of the vascular network in AD mice will be accomplished in Task 5. Finally, Tasks 6 and 7 will explore amyloidogenesis in both neuronal and vascular compartments in AD mice and the modulation by EE of hippocampal neurogenesis and epigenesis in extrahippocampal brains

regions in AD mice. Task 8 will consist in the dissemination of the results in meetings and in the form of publications in peer-reviewed journals.

The strength of our proposal resides in the fact that it is based on an integrative approach combining state-of-the art animal model of AD (partners 1 and 3), cellular imaging of activity-dependent genes (partners 1 and 2) and biomarkers of AD's progression (partners 1, 2 and 3), electrophysiology (in vivo LTP and single unit recordings)(partners 1), molecular biology and learning and memory function (partners 1 and 2) and confocal microscopy of the activity of blood vessels (partner 3). We anticipate that the work described in this project may open new avenues for clinical research in the field of human neurological disorders where application of EE paradigms, alone or in combination with pharmacological treatments, might emerge as a pertinent therapeutic strategy in the near future.

Partners Bruno BONTEMPI
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ANR funding 580 000€

Starting date and duration January 2011 - 43 months

Reference ANR-10-MALZ-001

Cluster label Prod'Innov

Abstract

Cognitive reserve (CR) has been postulated to mediate the relationship between age- or Alzheimer's disease (AD)-related pathology and the clinical impact of that pathology. However little is known about the neural implementation that may underlie CR.

Based on the hypothesis that CR can attenuate the effects of age-related neural changes via differential expression of functional MRI (fMRI) identified brain networks, the overall theme of the CRESCENDO (Cognitive REServe and Clinical ENDO phenotype) project is to identify the determinants of heterogeneity in cognitive aging by understanding to what extent CR contributes to explaining this heterogeneity, our approach combines brain imaging biomarkers, neuropsychological assessments, measurements of CR proxies, plasmatic biomarkers of amyloid charge and metabolic disorders.

The CRESCENDO project is an extension in time and scope of an existing epidemiological cohort: the ESPRIT cohort, which is a longitudinal study of cognitive and psychiatric disorders undertaken in France and supported by the ANR LongVie. Its aim is the construction of a comprehensive database incorporating clinical, biological, genetic and environmental risk factors. We plan to organise a new follow-up at 12-year including the 600 younger participants of the ESPRIT cohort.

The first objective of the project will be to investigate the neural implementation of CR by performing a task-related activation during the fMRI acquisition, adopting a strategy using a validated tool - the letter Sternberg cognitive activation task - particularly adapted to identifying patterns of load-related activation that are expressed as a function of CR in cognitive aging. Furthermore, the concept of CR has been proposed to help account for the apparent discrepancy between some determinants of ageing and measurable pathology assessed by structural MRI (sMRI) measurements and between the pathology and its clinical manifestations (e.g., cognition). To investigate this question we plan to carry out a large and detailed sMRI examination including assessments of global and regional atrophy, white matter lesions, microbleeds...

The second objective is to investigate whether the association between CR and cognitive decline is influenced by amyloid charge or lipids profile. To understand the potential impact of amyloid charge on cognitive ageing, we aim to first understand the interrelationships between the 10-year change in plasma A β 40 and A β 42 levels and sMRI and fMRI biomarkers and then to examine the association between measured CR and rate of cognitive decline according to the

levels of amyloid charge. Furthermore we will investigate to what extent lipids profile contribute to modify cognitive reserve and to understand whether this relationship is influenced by APOE genotype. In the absence of efficient treatment, this approach could lead to a strategy consisting in developing resilience to the pathological cascade by managing cerebral hypercholesterolemia.

We were able to benefit from the expertise of the extensive research work on CR carried out by our collaborators (Y. Stern ; R. Mayeux ; A. Brickman) at the Cognitive Neuroscience Division (the Sergievsky Center and the Taub Institute) of Columbia University, New-York, US. This close partnership between benchmark American and European Centres gives us the unique opportunity to approach the original CR concept by comparing two distinct population-based studies (WHICAP and ESPRIT).

This project will be conducted by both academic and industrial partners who are recognized experts in their fields: INSERM U888 specialized in academic research on brain aging, INTRASENSE, sme specialized in medical imaging solutions, and SysDiag a mixed academic (CNRS)-industrial (BIORAD) group in the field of the biological biomarkers. Moreover, all the partners will benefit from local facilities such as MRI imaging and supercomputing platforms.

Partners Stephane CHEMOUNY
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Coordinator Karen RITCHIE

ANR funding 655 000€

Starting date and duration March 2011 - xx months

Reference ANR-10-MALZ-007

Cluster label EuroBioMed (ex ORPHEME)

EPITAUDNA

Deciphering the role of nuclear Tau and the influence of ABeta oligomers. in neurons under physiological and stress conditions

Abstract

Alzheimer disease (AD) is the only neurodegenerative disease where both Abeta and Tau pathologies are associated. Until today, the mechanisms underlying the interplay between Abeta and Tau pathologies remain unresolved. To decipher these mechanisms remains an essential point to understand the etiopathology of AD. Tau is mainly known as microtubule-associated protein. A recent study performed in collaboration between our two teams highlighted a new function of Tau as an essential nuclear key player in the neuronal early stress response. In this work, we reported that oxidative and heat stress (HS) induced a reversible accumulation of dephosphorylated Tau in nuclei of neurons. Further, we demonstrated that dephosphorylated nuclear Tau was able to bind DNA and preserve neuronal DNA integrity under stress condition. Contrary to HS, cold stress increased Tau phosphorylation, prevented nuclear Tau accumulation and induced DNA damage. Abeta oligomers are now known to be the actors of Abeta toxicity. Abeta toxicity has been demonstrated to be mediated by Tau but the mechanisms underlying this relationship remain poorly understood. Altogether, hyperphosphorylation of Tau induced by Abeta might likely prevent nuclear Tau accumulation and impair the DNA protective role of Tau in stress condition. Given the capacity of Tau to form protein-DNA complexes, we cannot exclude that nuclear Tau could affect gene expression in neurons either by directly binding to regulatory DNA sequences and/or through regulation of the epigenetics of neurons. Therefore prevention of nuclear Tau accumulation mediated by Abeta oligomers could also impair Tau-regulated gene expression in stress condition and contribute to the etiopathology of AD. The double aim of the present project is to further explore the role of nuclear Tau respect to gene expression regulation and specific epigenetic modifications in the differentiated neurons under physiological and stress conditions and to analyze the influence of Abeta oligomers on these mechanisms. The specific goals are the following : 1) Analyze the binding capacity of nuclear Tau to endogenous neuronal DNA under physiological and heat stress conditions. Using ChIP assays, we will first focus on the capacity of Tau to interact with some specific loci, such as those DNA sequences that are present on the nuclear compartments where Tau has been observed in neuroblastoma and non-neuronal cells. Secondly, using ChIP-on-chip technique, we will analyze the capacity of Tau to interact with DNA genome-

wide with a special emphasis on promoter regions. Finally, we will try to determine the regions of Tau protein necessary to form protein-DNA complexes, using adenoviral vectors encoding either wild type or mutated forms of Tau. 2) Analyze the capacity of Tau to regulate gene expression. We will analyze the capacity of Tau to regulate gene expression respect to some specific loci (centromeric and pericentromeric sequences and rDNA genes). and we will analyze the effect of Tau genome-wide on the expression of mRNAs as well as on non-coding microRNAs using the corresponding microarrays. 3) Investigate the capacity of Tau to affect epigenetic mechanisms, mainly histone modifications. We will specially focus on the rate and distribution of diverse histone modifications (acetylation, methylation) marks associated to either gene silencing or transcriptional activation modifications. We will also analyze the effect of Tau on the expression and distribution of factors and cofactors regulating these histone modifications in neurons 4) Challenge the effect of Abeta oligomers on stress-induced nuclear Tau accumulation, Tau-DNA complex formation and nuclear Tau function. We will test if Abeta oligomers-induced Tau hyperphosphorylation impairs the ability of Tau to accumulate into the nuclei of neurons under stress condition. The capacity of Tau to bind DNA, regulate gene expression and modulate epigenetic mechanisms will also be evaluated.

Partners Eliette Bonnefoy

Coordinator Marie-Christine Galas

ANR funding 357 635€

Starting date and duration January 2011 - 36 months

Reference ANR-10-MALZ-006

Cluster label

MInAlpha7

Molecular imaging of nicotinic $\alpha 7$ receptors in Alzheimer's disease

Abstract

Alzheimer's disease (AD) is the most frequent progressive neurodegenerative disease representing the major cause of dementia in elderly subject. With 860000 people affected in France, it is a major public health problem. The diagnosis of AD is currently based on clinical criteria. The certitude diagnosis is assessed by the evidence of post-mortem characteristic brain lesions such as β -amyloid protein deposits, neurofibrillary tangles and neuronal loss. The exploration of these lesions in vivo using the method of molecular imaging with PET (positon emission tomography) will allow having a sensitive and selective diagnosis tool. This method requires tracers, or radiopharmaceuticals, specific of the molecular target to be explored (abnormal protein, receptor). The deposits of abnormal proteins (β -amyloid plaques, hyperphosphorylated tau) are targets of choice for AD. Radiopharmaceuticals allowing to localise and quantify them are currently proposed. Recent results showed that the density of β -amyloid plaques determined by PET can be related to the stage of AD, but other showed that this density is unable to predict the cognitive state of patients.

Another approach for obtaining a relevant diagnosis tool for AD is the measurement of changes in biological markers associated to dysfunctions of neurotransmission and neuronal death. The cholinergic neurons are strongly involved in the processes affected during AD and are relevant targets of current treatments. Modifications of cholinergic neurotransmission have been assessed using the PET tracer ^{11}C -nicotine, showing links between the density of nicotinic receptors and attention deficit. The functional exploration of cholinergic neurotransmission appears therefore as a promising approach for the early and selective diagnosis of AD. The nicotinic receptors of alpha7 subtype (alpha7R) play major roles during AD such as: changes in their density, formation of alpha7R- β -amyloid peptide complexes that are toxic for neurons, reinforcement of neuroinflammation that worsen neuronal lesions. To date, no PET tracer for alpha7R is available.

The objective of this project is to develop ^{18}F -labeled radiopharmaceutical(s) for the diagnosis and therapeutic follow-up of AD using PET molecular imaging of alpha7R.

The specific objectives are: 1) the conception and synthesis of new compounds targeting alpha7R, 2) in vitro evaluation of the pharmacological properties of these compounds (affinity, selectivity), 3) radiolabeling of selected compounds with ^{18}F , 4) evaluation of these ^{18}F -tracers in animal.

This project is based on the recognized expertise of the 2

partners in the field of:

1 Organic chemistry: ICOA (Orléans) is specialized in organic synthesis of compounds aimed at therapeutic use, and thus has all the expertise allowing to product a large panel of new compounds.

2 Radiochemistry, in vitro and in vivo pharmacology, SPECT/PET molecular imaging: the team 3 of Inserm U930 (Tours) has the expertise allowing the development of radiopharmaceuticals aimed at a preclinical and clinical use.

Preliminary results have already been obtained by both partners. On the basis of literature data which described compounds having affinity for alpha7R, we obtained new compounds belonging to 2 chemical families that showed nanomolar affinity for alpha7R. These first results lead to pursue and extend the development of new fluorinated compounds which, in function of their pharmacological properties will be labeled with 18F for further evaluation in animals.

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Coordinator Sylvie CHALON

ANR funding 354 662€

Starting date and duration February 2011 - 36 months

Reference ANR-10-MALZ-004

Cluster label

SOMADOLF

Somatostatin deficits in olfactory systems : early biomarkers of Alzheimer disease

Abstract

Somatostatin (SRIF) is a widely expressed neuropeptide in the brain involved in neuroendocrine, cognitive and sensory functions. Hippocampal and cortical somatostatinergic levels are consistently reduced in Alzheimer's disease (AD), being clearly associated with cognitive impairments. Recently, a primate-specific single nucleotide polymorphism (SNP rs4988514) present in the human somatostatin gene (SST) was reported to increase the risk of developing sporadic AD in Apolipoprotein epsilon 4-carrying patients in two distinct studies, suggesting that the genotype of the SST gene may impact SRIF expression and induce intermediate phenotypes linked to AD, such as Tau hyperphosphorylation.

Impaired olfaction is a landmark of the early stages of AD. It is detected sometimes before cognitive deficits, and is associated to the detection of neuropathological signs (neurofibrillary tangles) in olfactory structures. As cognitive impairment has been clearly associated to the extent of Tau pathology in hippocampal and cortical structures, a current hypothesis is that olfactory impairment may result from early neurodegeneration in the telencephalic structures that mediate olfactory processing. Surprisingly, whereas Tau pathology is indeed found in the olfactory bulb in all definite AD cases, whether it impairs its function has not really been investigated. Since somatostatin was recently shown to modulate olfactory processing, we hypothesize that olfactory somatostatinergic systems are altered during pathological aging of the olfactory system and that such an alteration is related to the decline of olfactory functions.

In vitro transgenic approaches will be used to evaluate the functional impact of the AD-related SST gene polymorphism on SRIF regulation. Transgenic mouse lines expressing the minimal human regulatory element will be developed and functionally characterized using olfactory and cognitive readouts, to test for the relevance of the SNP as an early biomarker of AD. In parallel, the vulnerability of olfactory SRIF systems to AD-related cytoskeletal changes will be evaluated in clinically-characterized post-mortem samples in relation with the SST SNP polymorphism. Finally a relevant experimental model for AD, the ThyTau22 mice, which displays progressive development of Tau pathology will be used to explore the functional relationships between olfactory SRIF levels, Tau hyperphosphorylation status and olfactory performances in order to further validate a novel animal model reflecting Tau and neuropeptide AD-related pathophysiology.

Partners	Michel SIMONNEAU LUC BUEE
Coordinator	Jacques EPELBAUM
ANR funding	680 000€
Starting date and duration	January 2011 - 36 months
Reference	ANR-10-MALZ-003
Cluster label	

SynflAD

Synaptic deficits and neuroinflammation in mouse models of Alzheimer's disease

Abstract

Intracellular accumulation of neurofibrillary tangles and senile plaques formed by the extracellular deposit of cerebral amyloid- β (A β) peptide oligomers are the classical pathological hallmarks of Alzheimer's disease (AD) and lead ultimately to neuronal cell death. However, it has become clear more recently that soluble A β disrupt glutamatergic synaptic function, which in turn leads to the characteristic cognitive deficits already present at early stages of AD. In addition, soluble A β is a potent activator of microglia and astrocytes leading to the production and the release of a whole array of inflammatory molecules which in turn affect synaptic transmission and plasticity.

There are two main inter-connected objectives to the project with the final aim to provide a rationale for the test and discovery of new therapeutic strategies to alleviate cognitive deficits that precede neurodegeneration in AD. First we will provide a comprehensive view of the structural and functional changes that occur at a central glutamatergic synapse during aging in two mouse models of AD. We will focus on synaptic transmission in pyramidal cells in the hippocampal CA3 area, a brain region critically involved in the encoding of novel information. Within this frame we shall ask the following fundamental questions : does chronic accumulation of A β -peptides over the progressive development of the disease impair synaptic structure, function and plasticity in the CA3 region of the hippocampus, a region critically involved in the encoding of novel information?

Second, we will study how neuroinflammatory processes participate in the progressive synaptic failure linking to cognitive deficits. Although it is well established that the neuroinflammation process participates both to the onset and the chronicity of AD, precise mechanisms linking neuroinflammation with glutamatergic synaptic disruption have not yet been explored. Is there a link between neuroinflammatory processes and synaptic dysfunction?

This project is a basic research project that will shed light on the pathological aging process in a brain region implicated in the encoding of novel information. However, we also plan to set the experimental conditions for examining how currently used therapeutic approaches (such as anti-inflammatory drugs or memantine) prevent all or part of the synaptic symptomatology found in AD transgenic mice. We will test if it possible to restore normal synaptic structure and function by chronic treatments with currently used therapeutic approaches (such as memantine), or new antiinflammatory

molecules?

The "synaptic failure" hypothesis of AD has received much less attention in France than in countries like UK or the United States. This is likely changing now given the high potential of drugs which could alleviate synaptic deficits in the early phase of the cognitive decline in AD. Our group has no previous participation in the field of AD, but it endeavours to durably make the field benefit from our strong expertise in synaptic electrophysiology and cell biology.

Partners

Coordinator Christophe MULLE

ANR funding 297 000€

Starting date and duration Months 20xx - xx months

Reference ANR-10-MALZ-009

Cluster label

TAU-STRUCT

NMR-spectroscopic characterization of the conformational changes of the Alzheimer-associated protein Tau induced by phosphorylation

Abstract

Alzheimer's disease (AD) is the most common form of dementia among older people, resulting in the formation of neurofibrillary tangles rich in Tau protein. The neurofibrillary tangles are formed from β -sheet rich paired helical filaments (PHFs) which are insoluble hyperphosphorylated aggregates of Tau protein. Physiologically, Tau is a microtubule-associated intrinsically disordered protein (IDP) occurring mainly in the axons of neurons. In its physiological form it acts to stabilize microtubules and to promote neurite outgrowth. The origin of the essential conformational transformation to the pathological form of the protein remains obscure. In this project we intend to study this conformational change at atomic resolution.

Our aim is to develop a self-consistent, atomic resolution molecular ensemble description of Tau that combines and reflects multiple complementary conformationally-dependent experimental parameters. We will use this description to examine the transition from apparent normality into the diseased state of Tau. In Alzheimer's disease, Tau becomes excessively phosphorylated, loses its ability to bind to microtubules and aggregates into neurofibrillary tangles that consist of paired helical filaments of Tau. The principal existing therapeutic strategies targeting tau in neurodegenerative disease include reducing tau phosphorylation through inhibition of specific protein kinases, and some transgenic animal studies have shown this to be a valid strategy. It is not known whether tau phosphorylation is necessary for aggregation, or whether tau aggregates before becoming phosphorylated. Deciphering the seminal changes in Tau structure that are induced by phosphorylation and drive aggregation therefore represents a major challenge of AD research inevitable to devise therapeutic strategies counteracting these toxic effects.

Key questions that will be addressed during the course of this project concern the chemical and environmental factors that induce conformational transition, in particular the conformational effects of high levels of phosphorylation.

The study of the complete Tau protein under conditions allowing the comparison of physiological and pathological environmental factors represents a major step forward in the understanding of the role played by this molecule in the development of Alzheimer's disease. The importance of a molecular ensemble description of this important protein for

human health may prove critical in establishing a bridgehead between physical chemistry and biology, and eventually medicine. Few research consortia worldwide currently find themselves in such a favourable position to undertake the proposed research project. Interest is likely to be high, both from the academic world, but also from the private sector. Development of pharmacologically active molecules that target intrinsically disordered proteins, especially those involved in neurodegenerative disease, will play a major role in future activity of the pharmaceutical industry, and the provision of molecular models for studying proteins such as Tau will attract considerable interest.

More generally the value of developing a robust molecular description of IDPs is potentially very high. Contemporary structural biology requires the development of novel techniques to allow the study of highly flexible systems, containing significant proportion of disorder. Such systems play important roles throughout cellular biology, and have so far proved very difficult to study in the context of their intrinsic conformational disorder. In this project we propose to develop techniques that allow the study of IDPs at atomic resolution, laying the foundations for a description of the molecular basis of protein function and malfunction even in the presence of high levels of disorder.

Partners**Coordinator**

Martin BLACKLEDGE

ANR funding

219 377€

**Starting date
and duration**

Months 20xx - xx months

Reference

ANR-10-MALZ-002

Cluster label