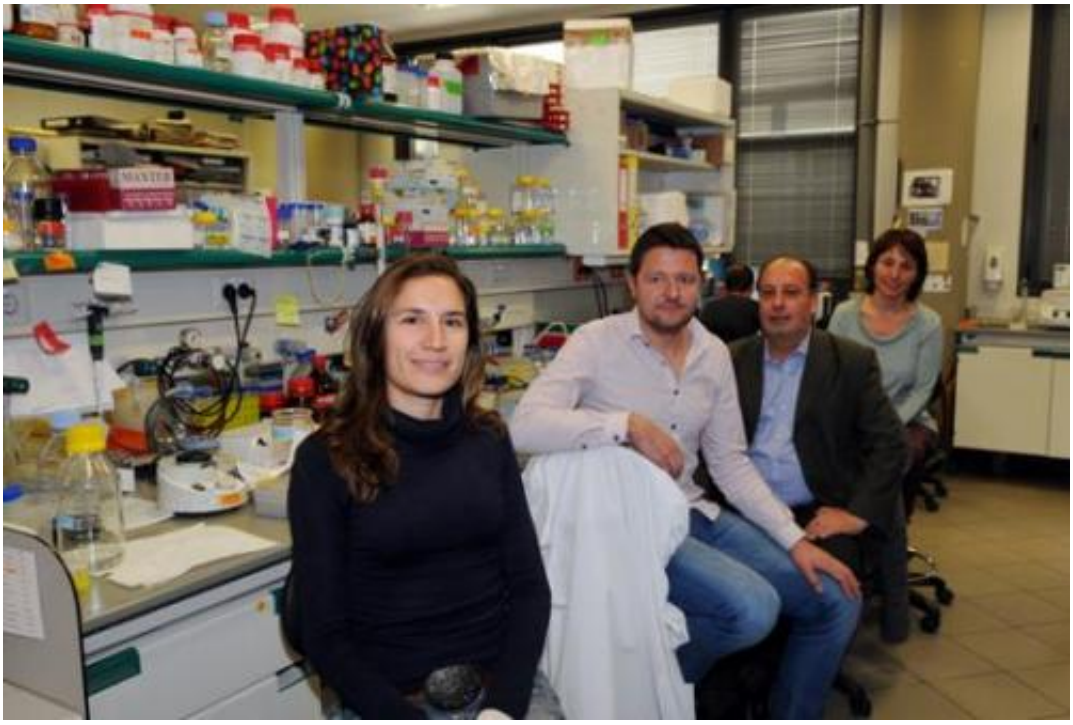
Reelin protein rescues cognitive deficits in an animal model of Alzheimer's disease

March 7 2014



From left to right, Daniela Rossi, Lluís Pujadas, Eduardo Soriano and Natàlia Carulla.

Reelin, a crucial protein for adult brain plasticity, recovers cognitive functions in mice with Alzheimer's disease. This is one of the main results of an article published on the journal *Nature Communications*, co-led by Eduardo Soriano, professor from the Department of Cell Biology at the University of Barcelona (UB) and member of the Centre for

Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), and researcher Lluís Pujadas (UB and CIBERNED).

The study is part of the PhD thesis developed by Daniela Rossi, co-author of the article together with Lluís Pujadas. Natàlia Carulla, from the Institute for Research in Biomedicine (IRB), collaborated actively in the research too. Other participants are: M. Rosa Andrés, Cátia M. Teixeira, Antoni Parcerisas, Ernest Giralt, Bernat Serra and Rafael Maldonado, and the institutions Research Center for Neurological Diseases Foundation (CIEN Foundation), Vall d'Hebron Research Institute (VHIR) and Pompeu Fabra University (UPF).

To recover cognitive functions in models of Alzheimer's disease

Alzheimer's disease is a neurodegenerative disease characterised by progressive cognitive deficits, synaptic loss and neuronal death. It is mainly associated with the formation of senile plaques (extracellular deposits of amyloid-β, Aβ) and the presence of neurofibrillary tangles (intracellular bundles of tau protein). The disease, which is the most common form of dementia in the elderly, affects more than 100,000 people in Catalonia and 500,000 in Spain, and causes progressive degeneration of patients' intellectual and cognitive functions.

This new preclinical study proves that an increase in Reelin brain levels avoids cognitive deterioration in mouse models of Alzheimer's disease. Moreover, Reelin delays amyloid-beta fibril formation *in vitro* and reduces amyloid deposits in mice with Alzheimer's.

The double pathway of Aβ peptide and tau protein

Professor Eduardo Soriano, head of the Research Group Developmental

Neurobiology and Neuroregeneration of UB, explains that "most studies on Alzheimer's disease search for therapeutic targets addressed to a certain process involved in the disease." On the contrary, "our study analyses the signalling pathway of Reelin—a synaptic and cognitive enhancer— that regulates the amyloid precursor protein (APP) and tau protein, which are both involved in basic processes of Alzheimer's disease."

Lluís Pujadas, first author of the article together with Daniela Rossi, points out: "We knew that Reelin is involved in the double regulating pathway of Aβ peptide and tau protein, but it was difficult to understand their interaction."

"The study shows a new mechanism that enables to understand better the link between both aspects of the disease," he adds. The investigation describes how Reelin, trapped into amyloid fibrils, loses its ability to promote plasticity; thus, Reelin overexpression may be beneficial.

The most toxic peptides in Alzheimer's disease

Experts also describe how Reelin interacts in vitro and reduces the toxicity of Aβ42 peptide, responsible for fibril formation and the aggregation of senile plaques. Reelin interaction with Aβ42 peptides —nowadays considered the most toxic— was not described to date. It is the first time that a study proves that the presence of Reelin reduces Aβ42 peptides toxicity," affirms Daniela Rossi, from the Department of Cell Biology of UB.

In vitro results show that Reelin interacts with Aβ42 peptide and delays fibril formation. Results were reproduced in a mouse model of Alzheimer's disease and it was observed that Reelin also reduces amyloid plaque formation. The study demonstrates for the first time that Reelin has a neuroprotective effect in neurodegenerative diseases, proved *in*

vivo in animal models, and provides a hypothesis to explain its neuroprotective potential.

Reelin: neuroprotective tool and cognitive enhancer

"The most striking result is that a brain plasticity promoter can rescue an Alzheimer's clinical phenotype in an animal model," says Eduardo Soriano. Cognitive deficits recovery takes place after the activation of a signalling pathway —Reelin signalling— which homeostatically regulates global neuronal function: cognition, neuronal plasticity, amyloid formation, etc. Soriano stresses that, as a research line, "this methodological approach on signalling pathways that control different features related to brain plasticity and Alzheimer's disease is more effective."

Alzheimer's disease causes remain unknown; only 1.5% of cases are congenital. In previous studies, the research group led by Dr Eduardo Soriano observed that Reelin was altered in Alzheimer's disease and that its role in intracellular signalling pathways was associated with neuronal survival. They also studied Reelin's role in different aspects related to adult brain physiological behaviour and the homeostatical potential of the protein. The article published in *Nature Communications* extends the search for therapeutic targets against Alzheimer's disease, and Reelin pathway deserves consideration as a therapeutic target for the treatment of Alzheimer's disease pathogenesis. In fact, researchers plan to have a system to identify chemical compounds that promote Reelin signalling in some months.

More information: "Reelin delays amyloid-beta fibril formation and rescues cognitive deficits in a model of Alzheimer's disease." Lluís Pujadas, Daniela Rossi, Rosa Andrés,Cátia M. Teixeira, Bernat Serra-Vidal, Antoni Parcerisas, Rafael Maldonado, Ernest Giralt, Natàlia Carulla & Eduardo Soriano. *Nature Communications*. Volume: 5, Article

number:3443 DOI: 10.1038/ncomms4443