Major breakthrough in Alzheimer research: Looking for Alzheimer's causes at cellular level

July 23 2010

(PhysOrg.com) -- Researchers from the University of Sydney's Alzheimer's and Parkinson's Disease Laboratory have achieved a major breakthrough by finding the causes of Alzheimer's disease at a cellular level and thereby identifying a potential therapy as a result.

The groundbreaking new study led by Professor Jürgen Götz and Dr Lars Ittner, based at the University's Brain and Mind Research Institute (BMRI), is published today in the prestigious international scientific journal *Cell*.

The researchers have discovered how a protein called TAU affects and mediates the toxicity of amyloid-b, which together with TAU causes the symptoms of Alzheimer's disease.

Professor Götz said this significant breakthrough made by Dr Ittner and their team has implications for how the disease develops and how it may be treated.

"Alzheimer's disease is a major health threat to Australia's aging population," he said.

"More than 250,000 Australians are currently diagnosed with dementia, with numbers reaching epidemic proportions. Of all diseases with a memory loss, Alzheimer's is the most prevalent, predicted to affect one

in 85 people globally by 2050."

"The main clinical feature of Alzheimer's disease is a progressive loss of cognition, accompanied by aggression and mood disturbance, and eventually, the patients need to be institutionalised. The toll of Alzheimer's disease on the patients, their families and the caretakers is enormous. And unfortunately, to date Alzheimer's disease is incurable."

"A handful of approved drugs provide if at all only very modest symptomatic relief, without curing the disease. Therefore, to develop effective treatments, it is absolutely necessary that the basic mechanisms underlying these disorders be understood. This was our challenge."

The brain of all Alzheimer's patients is characterized by two types of insoluble deposits; amyloid-b plaques and neurofibrillary tangles, the latter formed by the protein TAU.

In a milestone work published in Science in 2001, Professor Götz had already showed that the two hallmark proteins amyloid-b and TAU act together in disease, but their exact connection remained unexplained.

"It was always clear to me that finding this link could be the key to understanding the disease," Professor Götz said.

Dr Ittner said they focused on the relationship between the two, which produced a finding that challenges the accepted research paradigm.

"TAU was always thought to be a protein exclusively localised to the axons of neurons, but at the same time amyloid-b exerts its toxic effects at the dendritic site of the synapse, which is at the other end of the neuron," he said.

"The more data we obtained the clearer it became to us that TAU must

have an as yet unrecognised function in the dendrite, so finally we had to break with the dogma of TAU being an exclusively axonal protein."

It was this thinking that achieved the major breakthrough.

The researchers found that TAU is essential for the positioning of yet another protein, the kinase FYN, at the dendritic site of the synapse, which then renders the neuron vulnerable to amyloid-b.

"By genetically deleting TAU or introducing a non-functional variant of TAU, we found we could prevent the development of symptoms in mouse models of Alzheimer's disease."

"These mice showed normal survival and their memory appeared to be perfectly fine."

In the second part of the study, Professor Götz and Dr Ittner explored the potential of their discovery for a treatment of Alzheimer's disease.

"We translated our findings into a novel therapeutic approach by using a small peptide that mimics the effects of removing TAU from the synapse, and we were thrilled to see that this not only fully prevented the pathology in our Alzheimer's disease models but cleared their memory deficits," Dr Ittner said.

"Although there is still a long way to go we believe we may have found a way of treating Alzheimer's disease," adds Professor Götz.

This breakthrough has encouraged Professor Götz and Dr Ittner in their endeavours to find a cure for Alzheimer's disease. Their teams at the University of Sydney's renowned Brain and Mind Research Institute (BMRI) will continue in their determination to find a cure.

More information: Cell: www.cell.com/