

Discovery of molecular pathway of Alzheimer's disease reveals new drug targets

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The discovery of the molecular pathway that drives the changes seen in the brains of Alzheimer's patients is reported today, revealing new targets for drug discovery that could be exploited to combat the disease. The study gives the most detailed understanding yet of the complex processes leading to Alzheimer's.

Alzheimer's disease is associated with plaques made up of deposits of a molecule called amyloid between brain cells, which leads to the formation of <u>tangles</u> of twisted fibres made from a molecule called tau, found inside the brain cells. This causes the death of brain cells which is thought to bring about the symptoms of <u>memory loss</u> and <u>dementia</u>. Although it has been accepted for over twenty years that the progression of disease is driven by amyloid and results in <u>abnormal changes</u> in tau, the exact mechanisms of disease remain somewhat of a mystery.

Recent genome wide association studies have identified the gene for a molecule called clusterin as a susceptibility factor for late-onset Alzheimer's disease. Levels of clusterin are also known to be elevated in blood in patients with Alzheimer's from an early stage in the disease so the researchers wanted to find out what role it might play in the progression of disease.

The team, led by researchers at King's College London's Institute of Psychiatry, looked first in <u>mouse brain</u> cells grown in the laboratory and found that the presence of amyloid alters the amount of clusterin in these cells. Clusterin then acts to switch on a signalling pathway that drives the



changes in tau that are associated with the formation of tangles inside the cells, another hallmark of the disease. When this signalling pathway was chronically switched on in a <u>mouse model</u> of the disease, the researchers observed an increase in tangle formation and evidence of <u>cognitive</u> <u>defects</u>.

The study, published today in the journal <u>Molecular Psychiatry</u>, also looked in humans and detected the signature of clusterin activation in the brains of Alzheimer's patients but not in the brains of patients with other forms of dementia.

Dr Richard Killick from King's College London's Institute of Psychiatry said: "This is the first time we've been able to connect the molecular mechanisms behind the formation of amyloid plaques in the brain with the formation of tangles inside the brain cells, two of the defining features of Alzheimer's disease. Our research has given the most detailed picture yet of how the disease progresses and we hope it will offer leads for the development of new treatments."

The signalling pathway that is turned on by clusterin is called DKK1-WNT. It involves interactions between a number of different molecules that could prove to be useful targets for the development of new drugs.

Current treatments for Alzheimer's are focused on alleviating the symptoms and there is no therapy that can prevent the progression of disease.

Professor Simon Lovestone, also from King's College London's Institute of Psychiatry, who led the study, said: "We have shown that we can block the toxic effects of amyloid when we stop this signalling pathway in <u>brain cells</u> grown in the lab. We believe that if we could block its activity in the brains of Alzheimer's patients too, we may have an



opportunity to halt the disease in man. Indeed, we have already begun our own drug development programme to do just that and are at the stage where potential compounds are coming back to us for further testing."

The DKK1-WNT pathways has also been implicated in some human cancers and although there is no evidence for a direct link, the findings from this study mean that there could be an opportunity to make advances in Alzheimer's research by capitalising on knowledge that is being gained from cancer research, the authors suggest.

Dr John Williams, Head of Neuroscience and Mental Health at the Wellcome Trust, which helped fund this study, said: "We will see more and more people affected by Alzheimer's disease as our population ages. This study gives us a much-needed additional insight to the complex biology that contributes to the development of Alzheimer's, which is vital if we are to develop new treatments that are so urgently needed."

More information: R. Killick et al. Clusterin regulates b-amyloid toxicity via Dickkopf-1-driven induction of the wnt–PCP–JNK pathway. *Molecular Psychiatry*, 2012. <u>www.nature.com/mp/journal/vaop ...</u> <u>full/mp2012163a.html</u>

Provided by Wellcome Trust

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