New research opens new pathway for the treatment of Alzheimer's disease

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Scientists from VIB and KU Leuven have discovered a new target molecule for the development of a treatment against Alzheimer's disease. There is currently no cure for this disease. Many candidate drugs fail because they also target proteins essential to life. This discovery from Leuven could form a target for a treatment against Alzheimer's disease with fewer side effects and that suppresses the very first symptoms of the disease. This research will be published in the leading journal *Nature Medicine*.

Alzheimer's Disease is the most common form of dementia in the West. The damage to memory and mental function causes one of the most terrifying clinical pictures. The current drugs for Alzheimer patients support memory for a short time, but they do not stop the death of brain cells. Recent insights have shown that Alzheimer's disease causes biochemical changes in the brain many years before the symptoms of dementia are present. It is very important to develop drugs that can be taken at this early stage in order to prevent the disease.

Many candidate drugs have an effect on the ɣ-secretase complex. This complex cuts proteins at specific sites and plays an important role in the development of amyloid plaques, a pathological hallmark in of the brains of Alzheimer patients. Aberrant and excessive cleavage of the amyloid precursor protein by the y-secretase complex results in the accumulation and deposition of the β-amyloid protein in amyloid plaques.

However, the ɣ-secretase complex is also involved in cleavage of a series

of other proteins essential to life. As a result, many candidate drugs that act on the ɣ-secretase complex produce toxic side effects.

GPCRs are a family of proteins that serve as the targets of the majority of all currently marketed drugs. The Nobel Prize in Chemistry for 2012 was awarded to Dr. Robert Lefkowitz and Dr. Brian Kobilka for their groundbreaking work in this field and the many medical applications of this knowledge. It is known that GPCRs also play a role in the development of Alzheimer's disease, but it is not yet clear how GPCRs regulate the ɣ-secretase complex.

β-arrestins are a family of proteins that classically block or limit GPCR activation; however, it has been recently appreciated that β-arrestins also have additional functions. Therefore, Amantha Thathiah set up a study under the supervision of Bart De Strooper to examine the involvement of β-arrestins in the development of Alzheimer's disease.

The scientists succeeded for the first time in demonstrating that β-arrestin 2 plays a role in regulation of the ɣ-secretase complex function and in the development of Alzheimer's disease in an Alzheimer's disease mouse model. More specifically, β-arrestin 2 interacts with two GPCRs that are known to play a role in the development of Alzheimer's disease. Moreover, expression of β-arrestin 2 is also elevated in individuals with Alzheimer's disease.

This research opens a new pathway for the treatment of Alzheimer's disease. β-arrestin 2 inhibition could be beneficial in prevention of the adverse side effects currently associated with γ-secretase inhibition. Therefore, this study provides a previously unexplored avenue for the development of a treatment that can act at a very early stage of Alzheimer's disease.

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