Title: Presenilin and Gamma-Secretase

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Lay summary
We have identified unnatural peptides as a novel gamma-secretase inhibitor, that may potentially be a promising lead compound for drug development against Alzheimer’s disease (AD).

AD is a progressive dementing neurodegenerative disorder affecting over 25 million people worldwide. As the average age of the population increases, the number of AD patients is expected to quadruple by 2050. There is no cure for AD; current treatments focus on helping people by care in daily life, manage behavioral symptoms, and slow or delay symptomatic manifestations. This fatal brain disease was first described by German psychiatrist Dr. Alois Alzheimer in 1906. He reported the deposition of two abnormal structures, called “senile plaques” and “neurofibrillary tangles”, in the brain of a woman Auguste D in her early 50s, who suffered from dementia. Now these abnormalities are thought as prime suspects in damaging and killing neurons in the affected patients.

Senile plaques, that are deposited in the extracellular space of brain parenchyma, primarily contain amyloid-β peptides (Aβ). Several lines of evidence suggest that Aβ directly affects the integrity of the neuronal synapses in brain and is a putative primary culprit of AD. Aβ is generated by breakdown of amyloid-β precursor protein (APP) by two proteases, called the β- and the γ-secretases. Protease is an enzyme that chops proteins into pieces like molecular scissors. Thus, the drugs that inhibit these molecular scissors have been expected as mechanism-based therapeutics against AD.

Presenilin is a central catalytic engine of the gamma-secretase. Several pharmaceutical companies and academic laboratories including us have reported the presenilin-targeting compounds as the γ-secretase inhibitors. However, some adverse effects are presumed by the treatment of the γ-secretase inhibitors, as the γ-secretase cleaves other substrates that are physiologically and biologically important proteins.

To identify novel γ-secretase inhibitor without adverse effect, we tested several unnatural peptides on the γ-secretase cleavage. We found the β-peptide that mimics the structure of a part of APP as a novel, presenilin-targeting, γ-secretase inhibitor. This peptide abolished the Aβ production from brain neurons. Importantly, the β-peptide predominantly inhibited the APP cleavage, implying that this peptide is a promising lead compound for the drug discovery. Further modification of this peptide as well as testing in animal models would pave the way for the development of the drugs against AD.
without adverse effect.

Understanding the molecular mechanisms of the protease provide crucial information for the inhibitor design. However, the precise structural information as well as the mode of actions of the $\gamma$-secretase still remain enigmatic. Using chemical biological technique, we identified that this peptide directly targets the substrate binding site in presenilin. Further analyses of this peptide would shed light on the rational drug design for AD treatment.