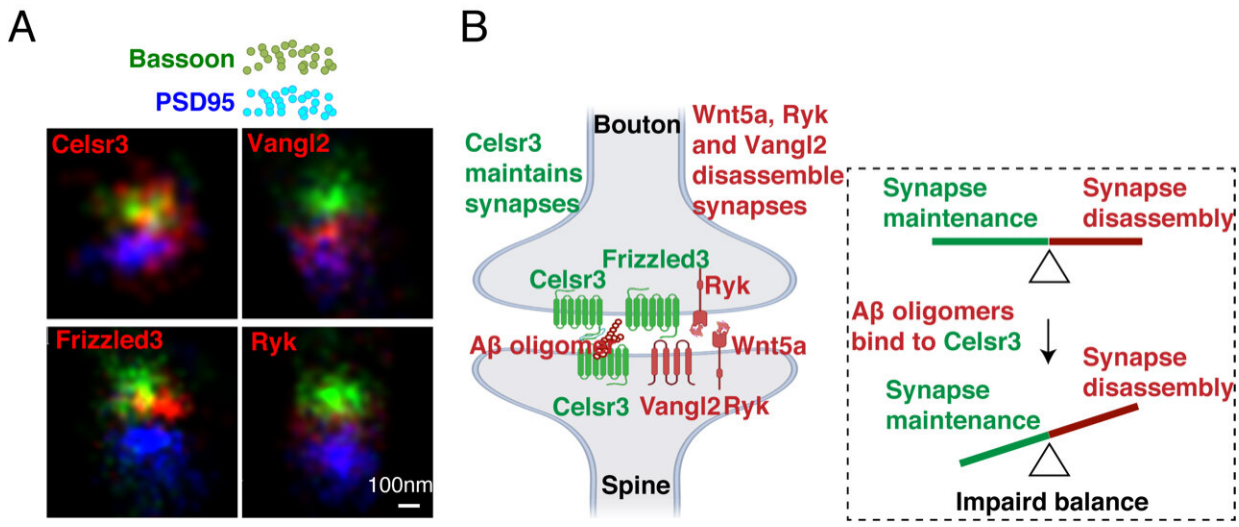
Researchers discover key mechanisms behind synapse degeneration in Alzheimer's brain

August 18 2021



A. Localization of Wnt/PCP pathway signaling components in glutamatergic synapses in adult hippocampus detected by super-resolution microscopy. B. Schematic diagram showing the balance of Wnt/PCP signaling in synapse maintenance and the binding site of oligomeric amyloid beta. Credit: Feng et al., *Sci. Adv*. 2021

Healthy adult brains are endowed with a vast number of synapses, structures that relay signals across nerve cells to enable communications, information processing and storage throughout the nervous system. Apart from dynamic periods when the brain is learning new information or skills, the number of the "glutamatergic" synapses, the major type of

synapses that neurons use to activate each other, largely remains constant in adults.

In brain disorders such as Alzheimer's, these synaptic connections, which hold our precious memories, are known to break down too early and disappear. This synapse degeneration is thought to start long before the loss of memory and accelerate as diseases progress. The causes of synapse degeneration in neurodegenerative disorders has not been well understood, mainly because scientists have not yet unraveled the key mechanisms that normally hold together these tiny structures (an average of one micrometer in diameter) throughout our lifetime.

Neurobiologists at the University of California San Diego have now uncovered the long-sought-after mechanisms behind the maintenance of glutamatergic synapses. Based on this fundamental discovery, Division of Biological Sciences Postdoctoral Scholar Bo Feng, Professor Yimin Zou and their colleagues have identified the main components driving amyloid beta-associated synapse degeneration. Amyloid beta are peptides of 36–43 amino acids derived from the amyloid precursor protein (APP) and are the main component of amyloid plaques found in the brains of people with Alzheimer's disease.

Despite tremendous efforts, drug discovery for Alzheimer's disease has not been successful. So far, the main approaches have been to either reduce amyloid beta production or clear amyloid beta plaques. The new discovery from UC San Diego researchers, published in *Science Advances* on August 18, 2021, suggests an alternative approach further downstream: protect synapses by directly blocking the toxic actions of amyloid beta.

Glutamatergic synapses are highly polarized structures with a presynaptic part from one nerve cell and a postsynaptic part from another. This type of polarity ensures the proper direction of

information flow. Zou's lab had previously found that during brain development the highly polarized synaptic structures are assembled by components of the planar cell polarity (PCP) pathway: a powerful signaling pathway that polarizes cell-cell junctions along the tissue plane. Using super resolution microscopy, the researchers detected the precise location of these same PCP signaling components, called Celsr3, Frizzled3 and Vangl2, in the glutamatergic synapses in the adult brain. They then found that removing these components, essential for the initial assembly of synapses from adult neurons, can dramatically alter the number of synapses. These surprising discoveries suggest that the overall synapse number in a normal brain is maintained by a fine balance between Celsr3 (which stabilizes synapse) and Vangl2 (which disassembles synapses).

Curious about whether these components are involved in synapse degeneration, they tested whether amyloid beta, a key driver of synapse loss in Alzheimer's disease, affects the function or interaction of these proteins. In a series of experiments, they showed that amyloid beta oligomers bind to Celsr3 and allow Vangl2 to more effectively disassemble synapses, likely by weakening the interactions between Celsr3 and Frizzled3.

"This is as if amyloid beta has long discovered the Achilles' heel of our synapses," said Zou, a professor in the Section of Neurobiology, Division of Biological Sciences.

When the researchers removed Vangl2 from neurons, they found that amyloid beta can no longer cause synapse degeneration both in neuronal cultures and in animals exposed to amyloid beta oligomers. Ryk, a regulator of the PCP pathway that interacts with Frizzled3 and Vangl2, is also found present in the adult synapses and functions in the same way as Vangl2 to mediate synapse disassembly. Blocking Ryk using function-blocking antibodies can protect synapses from amyloid beta-induced

degeneration, the researchers found.

To further test the hypothesis that this fundamental signaling pathway is a primary target of synapse degeneration in Alzheimer's disease, the Zou lab used 5XFAD mice, a well-known mouse model of amyloid beta pathology. This transgenic mouse carries five human mutations that cause Alzheimer's disease and therefore shows severe symptoms of synapse degeneration and cognitive function loss. They found that removing Ryk by gene knockout from adult neurons protected synapses and preserved cognitive function of 5XFAD mice. Infusion of the function blocking the Ryk antibody also protected synapses and preserved cognitive function in 5XFAD mice, suggesting the Ryk antibody is a potential therapeutic agent.

These exciting results suggest that the PCP pathway is a direct target of amyloid beta-induced synapse loss in Alzheimer's disease.

"As amyloid beta pathology and synapse loss usually occurs in early stages of Alzheimer's disease, even before cognitive decline can be detected, early intervention, such as restoring the rebalance of the PCP pathway, will likely be beneficial for Alzheimer's patients," said Zou.

Neuroinflammation, reflected by astrocyte and microglia activation, is also a hallmark of Alzheimer's pathology, which can be induced by amyloid beta accumulation and is known to accelerate synapse loss. Excitingly, the Zou lab found that the Ryk antibody can also block the activation of astrocytes and microglia in 5XFAD mice. Although they cannot distinguish whether this is due to the indirect effect of synapse protection or the blockage of Ryk functions in inflammation, or both, Zou believes that the results are consistent with the improved cognitive behavior and further support Ryk as a potential therapeutic target for both protecting synapses and reducing inflammation in Alzheimer's disease.

"This discovery may be applicable to synapse degeneration in general as the PCP components may be the direct synaptic targets mediating synapse loss in other neurodegenerative disorders, such as Parkinson's disease and Amyotrophic Lateral Sclerosis (Lou Gehrig's disease)," said Zou.

More information: Planar cell polarity signaling components are a direct target of amyloid β-associated degeneration of glutamatergic synapses, *Science Advances* (2021). DOI: 10.1126/sciadv.abh2307

Provided by University of California - San Diego