Suppression of Fli-1 protects against pericyte loss, could be new therapeutic target for Alzheimer's

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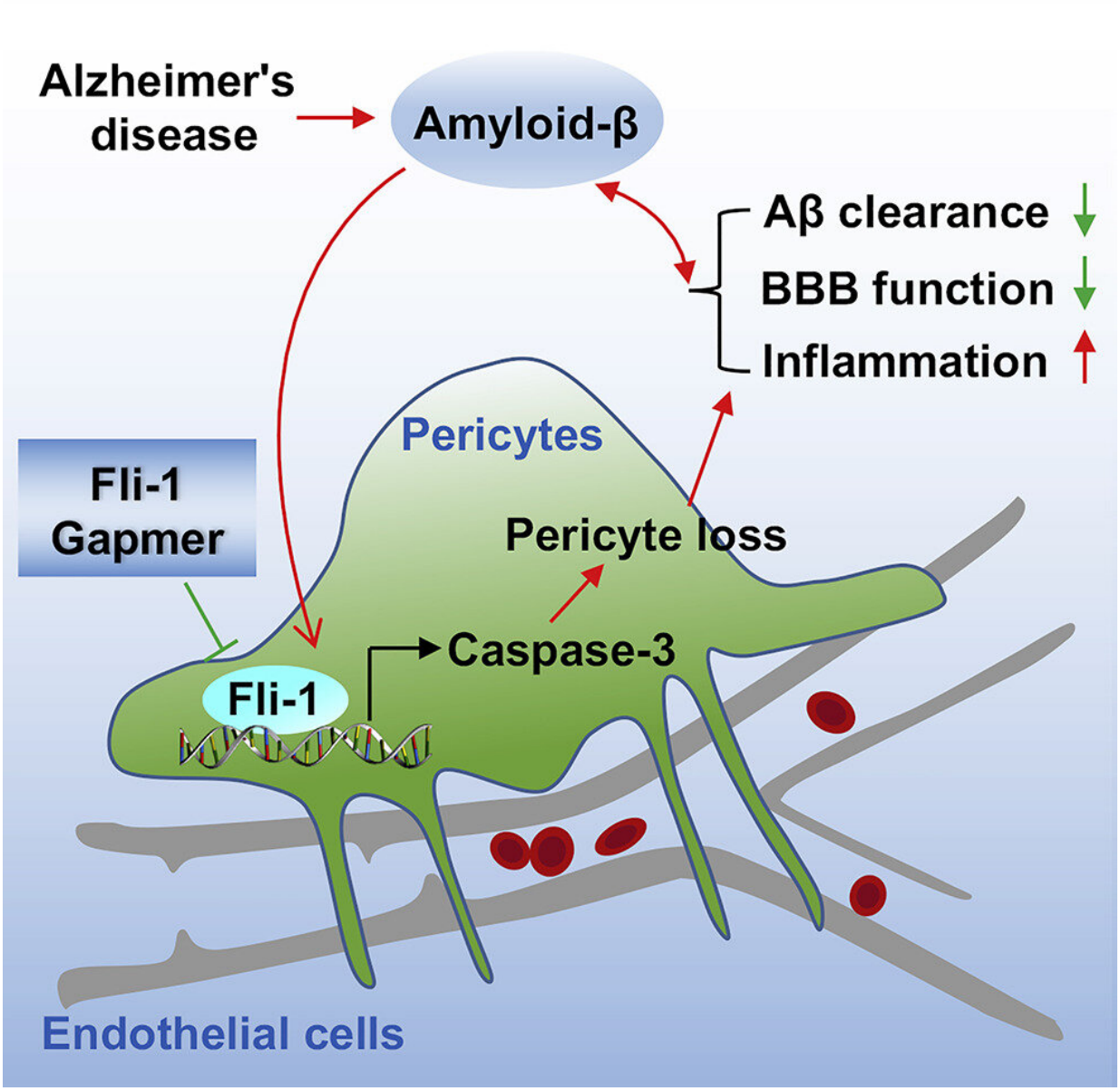

Graphical abstract. Credit: *Molecular Therapy* (2022). DOI: 10.1016/j.ymthe.2022.01.023

Alzheimer's disease is an enormous problem that, with an aging population, will only become bigger. More than 6 million Americans are living with Alzheimer's disease, and 1 in 3 seniors will die of it, according to the Alzheimer's Association. By 2050, the cost of Alzheimer's disease, currently estimated at $355 billion, will rise to $1.1 trillion.

Could one of the causes of such a huge and costly problem be traced back to the cells that line the body's tiniest blood vessels?

A new study published by a Medical University of South Carolina (MUSC) research team in *Molecular Therapy* suggests that the answer is yes. The team, led by Hongkuan Fan, Ph.D., associate professor in the Department of Pathology and Laboratory Medicine, found fewer of these cells, known as pericytes, in the brains of people who died of Alzheimer's disease. They also found higher levels of Fli-1, a protein most often found in blood cells and thought to govern their development.

When the team blocked, or inhibited, the action of Fli-1 in a mouse model of Alzheimer's disease, the memory of the mice improved. Blocking the protein also stopped immune cells from leaking into the brain and causing the inflammation that is a hallmark of Alzheimer's disease. Blocking Fli-1 could be a promising new approach to treating Alzheimer's disease and other dementias.

"We are really excited by these data because they suggest that Fli-1

could be a new therapeutic target for Alzheimer's disease," said Fan.

Better therapies for Alzheimer's disease are urgently needed. Most existing Alzheimer's therapies just treat the symptoms and do little to address underlying causes.

It has long been known that people who have vascular issues, or problems with their hearts or blood vessels, are at increased risk of developing Alzheimer's disease and other dementias. These include people who have had a heart attack or who have diabetes or high blood pressure or cholesterol.

That's not surprising, since the brain is hungry for oxygen. When it doesn't get enough, because the flow of blood is inadequate, its cells don't function as well and can begin to die.

Lining the walls of tiny blood vessels known as capillaries, pericytes make sure the brain's energy and waste-elimination demands are met.

"The capillary is where all the action is," said Perry Halushka, M.D., Ph.D., Distinguished University Professor of Cell and Molecular Pharmacology. "It is the place where all these exchanges really take place."

Pericytes also help to make up the blood-brain barrier that prevents impurities and immune cells in the blood from reaching the brain. They also help to remove amyloid-beta, known to be a culprit in Alzheimer's disease, from the brain.

When pericytes are lost, immune cells and impurities begin to leak into the brain, causing it to become inflamed and eventually leading to cell death and declining mental function.

"Pericytes may play a much more important role in dementia than people originally thought," said Halushka. "This is especially true in the aging population, where vascular dementia is going to become a bigger problem."

The MUSC team looked at the brains of people who had died of Alzheimer's disease, drawing on the resources of the brain bank at the Carroll A. Campbell, Jr. Neuropathology Laboratory.

"The opportunity to study the human brain is an extraordinary asset for the institution and for the study of all types of brain diseases, not just Alzheimer's disease," said Halushka.

The MUSC team found that the brains of people who died of Alzheimer's disease had 34% fewer pericytes than healthy brains in their hippocampus, a part of the brain associated with learning and memory. The remaining pericytes had much higher levels of Fli-1.

The team then showed that an animal model of Alzheimer's also showed pericyte loss in the hippocampus, increased Fli-1 and impaired memory. Blocking Fli-1 improved the mice's performance on behavioral tests meant to assess memory.

"The most exciting finding is that the Fli-1 inhibitor actually improved cognitive deficits in the animal model because, in the end, that's the only thing that matters," said Halushka.

The team also found that blocking Fli-1 in the mice helped to prevent pericyte loss and preserve the integrity of the blood-brain barrier as well as reduce the build-up of amyloid-beta.

"We didn't expect such a profound effect in the mice, but to our surprise, the inhibitor really worked," said Fan.

The next step for the MUSC team is to develop an RNA that could silence Fli-1 and so reduce the brain inflammation that leads to cell death in Alzheimer's disease. The goal would not be to do away with Fli-1, as it serves important roles in the body, but to maintain it at healthy levels.

"What's exciting is that this could be a new way to think about treating Alzheimer's disease, which has never been thought of before," said Halushka. "This research opens up a whole new area for potential targets, not just Fli-1 but the pericyte itself."

More information: Pengfei Li et al, Suppression of Fli-1 protects against pericyte loss and cognitive deficits in Alzheimer's disease, *Molecular Therapy* (2022). DOI: 10.1016/j.ymthe.2022.01.023

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