Could Alzheimer’s Stem From Infections? It Makes Sense, Experts Say

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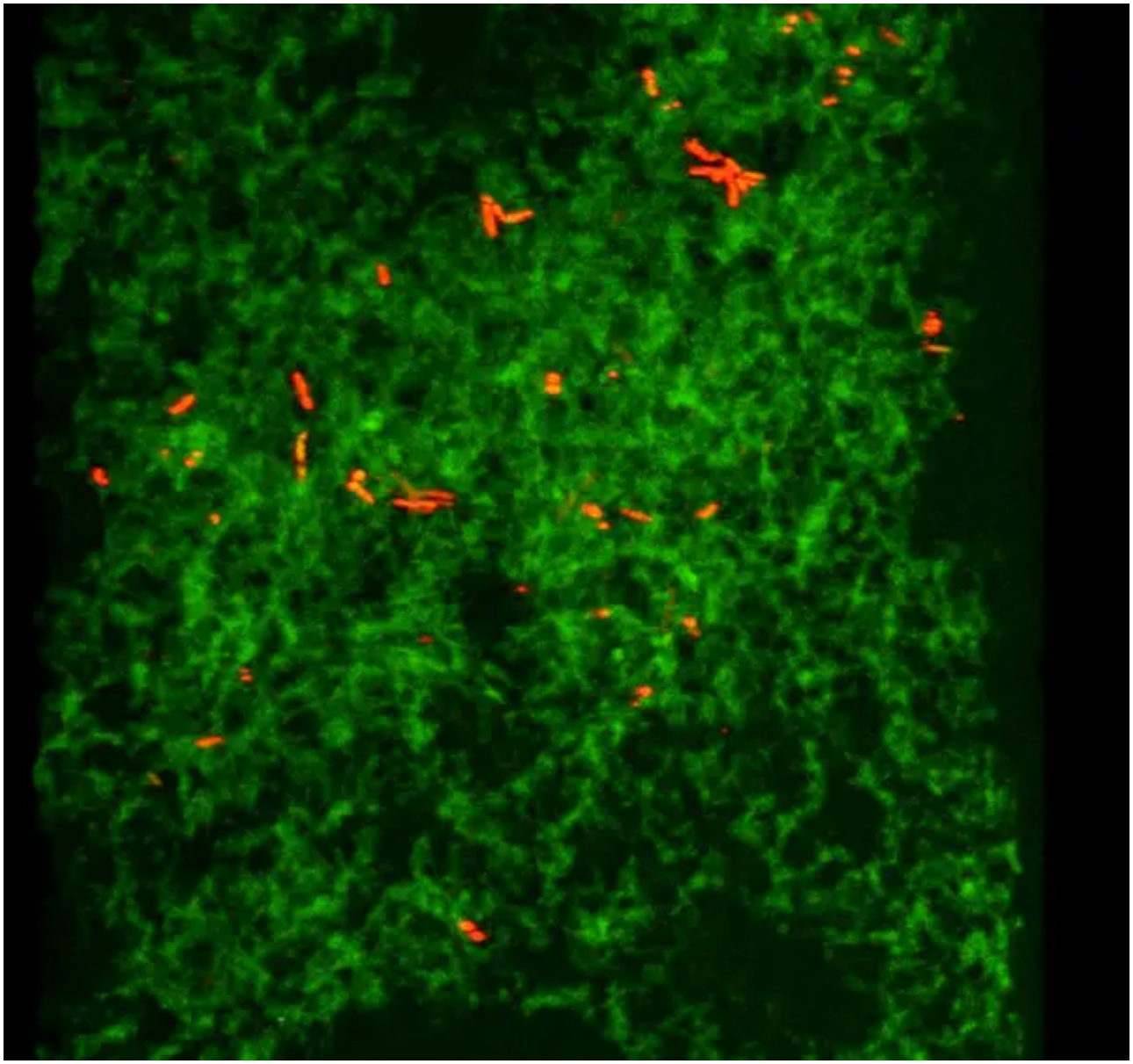

Salmonella bacteria, represented by the red spots, entrapped in a cage of proteins called beta amyloid, represented in green.Robert Moir and Rudolph Tanzi/Massachussets General Hospital and Harvard Medical School

Could it be that Alzheimer’s disease stems from the toxic remnants of the brain’s attempt to fight off infection?

Provocative new research by a team of investigators at Harvard leads to this startling hypothesis, which could explain the origins of plaque, the mysterious hard little balls that pockmark the brains of people with Alzheimer's.

It is still early days, but Alzheimer's experts not associated with the work are captivated by the idea that infections, including ones that are too mild to elicit symptoms, may produce a fierce reaction that leaves debris in the brain, causing Alzheimer's. The idea is surprising, but it makes sense, and the Harvard group's data, published Wednesday in the journal Science Translational Medicine, supports it. If it holds up, the hypothesis has major implications for preventing and treating this degenerative brain disease.

The Harvard researchers report a scenario seemingly out of science fiction. A virus, fungus or bacterium gets into the brain, passing through a membrane — the blood-brain barrier — that becomes leaky as people age. The brain's defense system rushes in to stop the invader by making a sticky cage out of proteins, called beta amyloid. The microbe, like a fly in a spider web, becomes trapped in the cage and dies. What is left behind is the cage — a plaque that is the hallmark of Alzheimer's.

So far, the group has confirmed this hypothesis in neurons growing in petri dishes as well as in yeast, roundworms, fruit flies and mice. There is much more work to be done to determine if a similar sequence happens in humans, but plans — and funding — are in place to start those studies, involving a multicenter project that will examine human brains.

"It's interesting and provocative," said Dr. Michael W. Weiner, a radiology professor at the University of California, San Francisco, and a principal investigator of the Alzheimer's Disease Neuroimaging Initiative, a large national effort to track the progression of the disease and look for biomarkers like blood proteins and brain imaging to signal the disease's presence.

Dr. David Holtzman, a professor and the chairman of neurology at the Washington University School of Medicine in St. Louis, was also intrigued. "It is obviously outside the box," he said. "It really is an innovative and novel study."

The work began when Robert D. Moir, of Harvard Medical School and Massachusetts General Hospital, had an idea about the function of amyloid proteins, normal brain proteins whose role had long been a mystery.

The proteins were traditionally thought to be garbage that accumulates in the brain with age. But Dr. Moir noticed that they looked a lot like proteins of the innate immune system, a primitive system that is the body's first line of defense against infections.

Elsewhere in the body, such proteins trap microbes — viruses, fungi, yeast and bacteria. Then white blood cells come by and clear up the mess. Perhaps amyloid was part of this system, Dr. Moir thought.

He began collaborating with Rudolph E. Tanzi, also at Harvard Medical School and Massachusetts General Hospital, in a study funded by the National Institutes of Health and the Cure Alzheimer's Fund. The idea was to see if amyloid trapped microbes in living animals and if mice without amyloid proteins were quickly ravaged by infections that amyloid could have stopped.

The answers, they reported, were yes and yes.

In one study, the group injected Salmonella bacteria into the brains of young mice that did not have plaques.

"Overnight, the bacteria seeded plaques," Dr. Tanzi said. "The hippocampus was full of plaques, and each plaque had a single bacterium at its center."

In contrast, mice that did not make beta amyloid succumbed more quickly to the bacterial infection, and did not make plaques.

For years, researchers had been fixated on the idea of plaques as a sort of trash that gathered in the brain. Few had asked if there might be some other explanation.

As Dr. Samuel E. Gandy, a professor of neurology and psychiatry at the Icahn School of Medicine at Mount Sinai Hospital in New York, explained, there was a long and persuasive body of research laying out the Alzheimer's pathway: Plaques form and set off the formation of tangled threadlike tau proteins. Then, as tangles of tau kill nerve cells, the brain becomes inflamed, resulting in the killing of many more nerve cells.

There were a few puzzling clues that something else might be going on, but they did not make much sense.

For example, Dr. Weiner said, some investigators reported that people who had developed Alzheimer's had higher levels of antibodies to herpes, an indicator of a previous infection, than people who did not have the disease.

"The suggestion that herpes was causative seemed a bit far-fetched," he said.

The new paper, Dr. Gandy and Dr. Weiner said, provides a plausible explanation.

Dr. Berislav Zlokovic, the director of the Zilkha Neurogenetic Institute at the University of Southern California, said his studies of the blood-brain barrier also fit well with the new hypothesis. When he discovered that the barrier started to break down with aging, he noticed that the leakiest part was the membrane that protects the hippocampus, the site of learning and memory. That is also where Alzheimer's plaques form.

Dr. Tanzi and Dr. Moir's hypothesis, he said, "is very hypothetical at this point, but it does make sense."

Of course, there must be more to Alzheimer's than the brain's innate immune system. What about people who have a mutated gene that guarantees they will develop the disease at an early age?

For them, Dr. Tanzi says, the problem is that they vastly overproduce beta amyloid. There is so much that it clumps on its own, without the presence of microbes.

Not everyone who has had a brain infection develops Alzheimer's, though. Why would some be more vulnerable than others? According to the new theory, it probably has to do with the brain's ability to clear out the balls of beta amyloid after they have killed microbes, Dr. Tanzi said. For example, it is known that people with a gene called ApoE2 have brains that are good at sweeping out plaque, and have a low risk of Alzheimer's in old age. Those with a different version, ApoE4, are inefficient in removing plaque and have a high risk of Alzheimer's.

Recent data suggests that the incidence of dementia is decreasing. It could be because of better control of blood pressure and cholesterol levels, staving off ministrokes that can cause dementia. But could a decline in infections also be part of the picture?

"That's a possibility," Dr. Weiner said.

At this point, the Harvard researchers have what many say is an intriguing hypothesis, but they readily acknowledge that much work lies ahead.

The Cure Alzheimer's Fund is starting a large collaborative project that will use gene sequencing technology to carefully look for microbes in brains from people who had Alzheimer's and those who did not. Researchers will also look for microbes in plaques found in human brains.

That, though, "is a big, big second step," Dr. Tanzi said. "First, we need to ask whether there are microbes that may sneak into the brain as we age and trigger amyloid deposition."

"Then," he said, "we can aim at stopping them."

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