EXCITING FIND in Alzheimer's research

Neurons die earlier than experts previously thought in Alzheimer's disease, and stopping the process could prevent the disease from ever developing, finds a new study from Tokyo Medical and Dental University in Japan. This has been reported in Medical News Today.

Alzheimer's disease is the leading cause of dementia, and as many as 5-million people in the United States live with the disease. It causes a range of symptoms that begin with memory loss and confusion before progressing to difficulties with orientation, thinking, and speech.

There is currently no cure for Alzheimer's, and the exact cause of the disease remains unclear. However, scientists have found sticky clumps of a protein called beta-amyloid in the brains of people who have died of the disease. This protein has been a major target for research to date.

So far, trials of drugs that target beta-amyloid have been unsuccessful. Some scientists think that this is because the treatments have started too late.

They believe that the process leading to Alzheimer's disease starts many years before diagnosis and that once people join clinical trials, it may be too late to help them. The early stages of the disease, therefore, represent a critical window in which to intervene.

The critical window

To find out what is happening in the brain before Alzheimer's disease develops, researchers from Tokyo Medical and Dental University began looking at an earlier phase of cognitive decline called mild cognitive impairment (MCI).

MCI describes the small changes to brain function — such as forgetting the names of items or losing things more often than usual — that can occur before Alzheimer's disease.

Although it is not always the case, people with MCI are more likely to develop Alzheimer's disease later. Due to this, researchers consider it to be a window into the very early stages of the illness.

From mouse to man

In the current research, which features in Nature Communications, the scientists measured neuronal death — a key process underlying the symptoms of dementia — in mouse models of Alzheimer's disease, as well as in people with MCI and those with Alzheimer's disease.

They measured how many neurons had died using a protein called HMGB1, which dying neurons release. They measured the levels of this protein in the fluid surrounding the spinal cord of 26 people with MCI and 73 people with Alzheimer's disease.

The researchers also carried out an innovative new test, using a new biomarker called pSer46-MARCKS to detect dying neurons at different stages of the disease in the brains of Alzheimer's disease model mice and people with MCI.

"Neuronal death is obviously very important in the development of Alzheimer's but is notoriously difficult to detect in real time because dying cells cannot be stained using chemical or immunohistological methods," explains the lead author of the study, Hikari Tanaka.

The researchers were surprised to find that neurons died much earlier than they expected. In fact, the participants with MCI had more neuronal death than those with Alzheimer's disease.

Trapped YAP

The scientists may also have discovered what causes neurons to die so early in the disease process, suggesting that a protein called YAP is responsible.

Previous genetic studies have found a link between YAP and Alzheimer's disease. YAP, which regulates neuronal death, was present in lower levels in people with MCI.

Interestingly, the researchers found the missing YAP trapped inside clumps of beta-amyloid — the deposits that have the most well-known association with Alzheimer's disease. This finding may change how scientists think about Alzheimer's disease.

The popular opinion among scientists is that the beta-amyloid protein is the first trigger for Alzheimer's disease, leading to the death of neurons. They call this the amyloid hypothesis.

However, these new findings suggest that the loss of the YAP protein — which happens before amyloid builds up in the brain — might be the main cause of neuronal death.

"This discovery might change the amyloid hypothesis," says senior author Hitoshi Okazawa.

A new treatment option?

But what does this mean for patients? Excitingly, the researchers believe that their findings could lead to a new treatment for Alzheimer's disease.

"By showing that neuronal [death] is YAP-dependent and begins prior to the onset of most symptoms, we predict that novel Alzheimer's disease therapies will be developed," says Okazawa.

To test a potential treatment, the team gave the mice gene therapy to replace the missing YAP protein. The treatment stopped the animals' neurons from dying, improved cognitive function, and even prevented beta-amyloid plaques from forming.

"[...] observing the almost transformative effects of YAP supplementation was hugely exciting," Okazawa continues. Although this is a very promising discovery, the researchers have not yet performed these experiments in people, and they will need to resolve important safety issues before they can do this.

The researchers also say that their method of measuring dying neurons could make it easier for doctors to diagnose people with MCI or Alzheimer's disease. Currently, no objective biomarkers are available to aid the diagnosis of MCI.

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