IISc team identifies an early-stage biomarker for Alzheimer's

In genetically altered mice, F-actin level decreased when animals were one month old.

Researchers at Bengaluru's Indian Institute of Science (IISc) have identified a potential biomarker for Alzheimer's disease. The biomarker shows up very early in the disease process and well before clinical and even pathological manifestation of the disease. They also found that it is possible to reverse the disease process if identified early.

Loss of dendritic spines from the surface of a nerve cell is already recognised as an early feature of Alzheimer's. But the underlying mechanism behind this loss was not known. Now, a team led by Vijayalakshmi Ravindranath from the Centre for Neuroscience at IISc has deciphered it. The results were published in *Journal of Neuroscience.*

Projections on the dendrites called spines grow or shrink in response to activity-dependent modification and correlates with normal memory or memory deficit in animal models.

Filamentous actin (F-actin) is a cytoskeletal protein which is responsible for maintaining the shape of the spines. While F-actin is formed by polymerisation of monomeric globular-actin (G-actin), depolymerisation leads to loss of F-actin and, in turn, the loss of spines. F-actin is crucial for memory consolidation.

"In mice that are genetically altered to have Alzheimer's, there was decreased F-actin protein level and increased G-actin protein level in animals as young as one month," says Reddy Peera Kommaddi, a DBT-Ramalingaswami Fellow, from the Centre for Neuroscience at IISc and first author of the paper. The change in the ratio of F-actin and G-actin led to loss of spines. The decrease in F-actin level and loss of spine thereof translated into memory deficit when the animals turned two months old.

In contrast, the first signs of memory deficit in mice with Alzheimer's is typically seen only when the animals are seven-eight months old. This is because the formation of protein clumps called amyloid plaques, which is one of the earliest clinical symptoms, happens at this stage.

Testing memory

To test the role of F-actin in behaviour response, two-month-old mice were exposed to mild foot shocks when kept in a conditioning chamber to bring about contextual fear conditioning. While normal mice placed in the chamber the next day they tend to freeze in anticipation of a shock, mice with Alzheimer's did not exhibit this behaviour. "The Alzheimer mice did not associate the aversive event [electric shock] with context but simply kept exploring the chamber," says Smitha Karunakaran from the Centre for Brain Research at IISc and a coauthor of the paper.

To test if decrease in F-actin protein and, in turn, the spine was responsible for deficit in memory a chemical was injected into Alzheimer mice to stabilise the level of F-actin. "A day after the injection, the F-actin level was restored to normal level and the Alzheimer mice showed increased freezing response just like healthy mice," says Dr Karunakaran.

The researchers went a step further to test the role of F-actin level in behaviour response by injecting a chemical into four-month-old normal mice. Since the chemical inhibits actin polymerisation, there was a decrease in the F-actin level. And the mice, though healthy, displayed significant decrease in freezing response, just like Alzheimer's mice would behave.

“These two experiments conclusively proved that loss in F-actin level leads to early behavioural changes that would eventually lead to Alzheimer’s disease,” says Dr. Kommaddi.

The team checked the level of F-actin levels in cortical brain tissue samples of human subjects who had Alzheimer’s, mild cognitive impairment and normal cognition. There was “graded lowering” of F-actin levels from normal to mild cognitive to Alzheimer’s tissue samples.

The correlation seen between mouse model and human disease indicates the potential to use F-actin levels as a biomarker.

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