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Cancer protein's surprising role as memory regulator

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Scientists at Dana-Farber Cancer Institute and Harvard Medical School have found that a common cancer protein leads a second, totally different life in normal adult brain cells: It helps regulates memory formation and may be implicated in Alzheimer's disease.

Cyclin E is a well-known culprit that drives many types of solid tumors and blood cancers. The report, published online in *Developmental Cell*, is the first revelation that cyclin E has a crucial role in the formation of nerve connections, or synapses, in the brain. Synapses are tiny connections between brain cells where memories are stored.

"This protein has a double life," said Peter Sicinski, PhD, a cancer biologist at Dana-Farber and senior author of the publication. "It is overexpressed in many different cancers, but it also is expressed in high levels in the human brain. We have found that cyclin E is needed for memory formation and is a very important player."

The researchers found potential evidence linking cyclin E to Alzheimer's disease, because it binds to an enzyme called Cdk5 that is involved in memory.

"There is good evidence that hyperactivity of Cdk5 contributes to Alzheimer's disease and inhibiting this enzyme can ameliorate symptoms in animals," said Sicinski, who is also a professor of Genetics at Harvard Medical School. "Manipulating cyclin E levels might be another way to accomplish this."

The scientists didn't test cyclin E in Alzheimer's mice, but they did show that when cyclin E binds to Cdk5 molecules, it locks them away in an unusable form. Moreover, when the researchers reduced cyclin E levels in mouse brain cells, fewer nerve connections formed and the animals' memories suffered.

Cyclins are a family of related proteins found in dividing cells. They serve as biological switches, controlling a cell's progression from one phase of its life cycle to the next. The actual signals to exit one phase and enter the next are issued by enzymes called cyclin-dependent kinases, or Cdks, that bind to cyclins.

Many types of cancer cells, including breast, ovarian, colon, and blood cancers, are driven by the overexpression of cyclin E, which acts like a car's accelerator pressed to the floor, speeding the cells through their growth-and-division cycle and allowing tumors to form and spread.

Though cyclin E is mainly found in dividing cells, researchers discover about a decade ago that cyclin E is also plentiful in adult, differentiated brain cells. But what it was doing there, no one knew.

In the current Developmental Cell paper, Junko Odajima, PhD, a postdoctoral fellow in the Sicinski laboratory and the paper's co-lead author (with Zachary P. Wills, PhD, from Harvard Medical School), showed that cyclin E in the brain attaches itself to the Cdk5 enzyme. When cyclin E molecules bind to and inactive Cdk5, synapses formation is increased, and, presumably, memory function improves.

Odajima tested this idea using a standard memory and learning test in which mice swimming in water must find a submerged platform to rest on, and remember its location in subsequent trials. The researchers then move the platform, requiring the animals to "forget" its previous location and learn and remember the new one.

As their hypothesis had suggested, mice deficient in cyclin E performed worse than rodents who had a normal amount of cyclin E. This contrast highlighted the importance of cyclin E for learning and memory.

Whether cyclin E levels rise and fall in the mouse brain during learning tasks is a topic of further research, said the scientists, who also plan to determine whether abnormal cyclin E levels can be linked to neurological diseases and learning disorders.

Provided by Dana-Farber Cancer Institute

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