

Cellular 'brakes' may slow memory process in aging brains

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University of Florida researchers may have discovered why some brain cells necessary for healthy memory can survive old age or disease, while similar cells hardly a hairsbreadth away die.

The discovery, published online ahead of print in the Nature publication Cell Death & Differentiation, could help scientists understand and find solutions for age-related memory loss.

Scientists with UF's Evelyn F. and William L. McKnight Brain Institute describe how they analyzed two neighboring regions of a tiny brain structure called the hippocampus in rats of varying ages. They found that a recently discovered enzyme known as PHLPP, pronounced "flip," may be silencing a vital cell-survival protein in the region where neurons are most susceptible to damage and death.

"The question is why does one set of brain cells live and another set die when they are only millimeters apart in the same small brain structure?" said Travis C. Jackson, a graduate student working with Thomas C. Foster, Ph.D., the Evelyn F. McKnight chair for research on aging and memory at UF. "We looked at an important signaling pathway that tells cells to stay alive or die, and the enzymes that regulate that pathway. Implicated in all this is a new protein that before a couple of years ago no one actually knew much about."

The scientists focused on the hippocampus, an anatomical region shaped something like a curved kidney bean in mammals. The structure is

widely believed to be central to the formation of memories, as well as an important component of motivation and emotions. A portion of it is known to be especially vulnerable to decreased cerebral blood flow, which can occur because of stroke or circulatory problems. The same area is also one of the earliest brain regions to show pathology associated with Alzheimer's disease.

Researchers studied both regions for signs of AKT, a protein that when activated, actually hinders many naturally occurring inducers of cell death. They found activated AKT was scarce among the cells that are vulnerable to damage and death and more abundant within the hardier cells.

The next step was to figure out what was turning off AKT in the vulnerable cells, which led scientists to PHLPP1, a recently discovered enzyme that is believed to be a natural tumor suppressor. Where PHLPP1 levels were high — which corresponded to the area with the vulnerable cell population — AKT activation was far less robust.

"Possibly, we have found a target that could be manipulated with drugs so that these brain cells can be saved from threats," said Foster, a professor of neuroscience at the UF College of Medicine. "If one area of the hippocampus has a deficiency in cell-survival signaling, it is possible to find a way to ramp up the AKT protein. The caveat is, there are studies that show over-activating AKT may not be good for memory — AKT may be naturally lower in this region for an important reason. But in times of intense damage, there may be a therapeutic window to upregulate AKT and get some benefit to health."

PHLPP was discovered in 2005 by a team of researchers led by Alexandra Newton, Ph.D., a professor of pharmacology at the University of California, San Diego, who had set out to learn what was controlling AKT-driven cell growth, proliferation and survival. The investigation led

them to PHLPP, which, in addition to being involved in healthy cellular processes, is known to propel tumor growth.

"Basically, PHLPP is important in controlling whether cells survive and proliferate or die," said Newton, who did not participate in the UF research. "If you want cells to survive brain disease, diabetes or heart disease, you want active AKT signaling and therefore low PHLPP. But if you want to stop cells that have the 'go' signal, like cancer cells, PHLPP can function as a brake. In this case, it appears as if there is an area in the hippocampus that is easily stressed and might undergo ischemia easily, because PHLPP is not allowing the AKT survival mechanism to work."

Source: University of Florida

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