

Alzheimer's disease as a case of brake failure?

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A loss of protein function in neurons may lead to dementia

Rutgers researcher Karl Herrup and colleagues at Case Western Reserve University have discovered that a protein that suppresses cell division in brain cells effectively "puts the brakes" on the dementia that comes with Alzheimer's disease (AD). When the brakes fail, dementia results.

This discovery could open the door to new ways of treating Alzheimer's disease, which affects up to half the population over the age of 85.

Determining the protein's previously unsuspected role in AD is an important piece of the puzzle and it brings a new perspective to the basis of AD. "It changes the logic from a search for a trigger that kicks off the dementia to the failure of a safety that has suppressed it," Herrup said.

The researchers reported their findings in the in the June 24 *Proceedings of the National Academy of Sciences* (PNAS). The paper was previously available online in the PNAS Early Edition.

Herrup has spent a good part of his career seeking to unravel the mystery behind unrestrained cell cycling. Looking at AD through the lens of cancer, Herrup sees the rampant cell division associated with cancer mirrored in AD-related dementia.

In cancer, the seemingly uncontrollable cell division enables the disease to overwhelm normal body cells. Adult neurons, or nerve cells, don't normally divide. (Cancerous brain tumors do not grow from neurons but

from glial cells.) Instead of producing new neurons in the brain, the cycling leads to cell death, which causes progressive dementia.

"Every cell wants to divide, and that basic urge never leaves the cell," Herrup said.

"Homeostasis in the brain has worked out a way to successfully suppress cell cycling, but with age even that highly successful program sometimes fails, resulting in a catastrophic loss of neurons."

Herrup's team experimented with a protein family known as cyclin-dependent kinases (Cdk). These enzymes power the cell cycle, driving it forward through its various phases. The scientists focused on one particular kinase – Cdk5 – termed "an atypical kinase" because they could find no involvement in propelling the cell cycle. They found that while it appears to be inert as a cell cycle promoter, Cdk5 in the nervous system actually functions to hold the cell cycle in check.

"Its mere presence helps protect the brain," Herrup said. "What we discovered is that Cdk5 acts as a brake, not a driver."

Their latest laboratory research examined the workings of Cdk5 in human AD tissues and in a mouse model. Normally, the protein resides in the nerve cell nucleus, but in the presence of AD – both in the mouse model and in the human tissue – the disease process drives the protein out into the cell's cytoplasm. This disrupts the status quo, overrides the brake and unleashes a chain of events that ultimately leads to the death of the cells and the resulting dementia.

"The ejection of Cdk5 out of the nucleus is probably related to the changed chemistry of the Alzheimer's brain and chronic inflammation that accompanies AD," Herrup said.

Source: Rutgers University

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