Scientists Discover Brain's Guardian Protein

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Hopkins scientists who have spent years killing off brain cells to figure out why and how they die now say their investigations have also shed light on how the brain defends itself.

Using mouse brain cells in a lab dish as well as whole animals, the researchers discovered that a protein, nuclear factor I-A (Nfia), is a central cog in a complex survival mechanism that preconditions brain cells to endure subsequent injury. Nfia is a so-called transcription factor that controls genes and other proteins.

Their finding appears in the June online edition of the Journal of Clinical Investigation.

In their experiments, the Johns Hopkins team exploited the fact that when mouse brain tissue is subjected to a stressful but not lethal insult — the equivalent of stroke in a dish — a defense response occurs that protects cells challenged by a more severe insult. The scientists dissected this so-called preconditioning pathway and the proteins that make it happen to identify the most critical molecular players, of which Nfia is one, they said.

“Identifying these molecules might someday lead to drugs that trigger this brain survival mechanism when people have a stroke or Parkinson’s disease,” said Valina Dawson, professor of neurology and neuroscience in the Johns Hopkins Institute of Cell Engineering.

“Our goal in studying these preconditioning molecules is to find

something that was protective not just of one kind of brain cell, but of all kinds," she says.

The technique she and her team used included exposing mouse brain cells to short bursts of a toxic chemical then screening this preconditioned material for genes that turned on as a result of the insult. Eventually, they compiled a list that included Nfia.

Focusing on Nfia, the researchers turned up the volume of this gene's expression in the cells during exposure to the toxic chemical that induced preconditioning, and next turned it down, noting that cells deficient in Nfia didn't survive but those with more did much better.

In another series of experiments, this time using whole mice, the team injected a toxic chemical into the brains of a control group of "normal" mice and also into a group that had been genetically engineered to produce less than the normal amount of Nfia protein. The mutant mice lacking Nfia were much more susceptible to brain cell death.

More information: Journal of Clinical Investigation: www.jci.org/

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