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Controlling Growth of Neural Stem Cells

Researchers have discovered that a gene previously implicated in a variety of forms of cancer is also a key regulator of neural stem cell proliferation. Understanding how the protein expressed by the gene *PTEN* promotes the proliferation of neural stem cells could aid efforts to use stem cells in treating neurological disorders.

Howard Hughes Medical Institute investigator Hong Wu and colleagues at the UCLA School of Medicine reported on the regulatory role of Pten in the November 1, 2001, *Science Express*, the online counterpart of the journal *Science*.

According to Wu, *PTEN* is the second most frequently deleted tumor suppressor gene, giving rise to human cancers including brain, breast, prostate, and endometrial cancers. There was also evidence, said Wu, that the PTEN protein played a normal role in neural development. "It was known that humans who have inherited deletions or mutations of the *PTEN* gene often showed macrocephaly, or abnormally large brains," she said.

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- Hong Wu

The gene is expressed in the central nervous systems of developing human and mouse embryos, but there were no detailed studies that looked at PTEN's role in the nervous system.

Knocking out the gene in mice caused early death, before significant brain development had occurred. So, Wu and her colleagues used the Cre-loxP system to genetically manipulate the mice so that the gene would be knocked out later in gestation. The researchers discovered that knocking out *Pten* in

the mouse embryos appeared to hyper-activate a signaling pathway that regulates cell proliferation and cell death in the brain.

Anatomical studies revealed a significant increase in brain size in the mutant animals. The researchers also noted an increase in the size of the brain cells themselves – the first evidence that the PTEN protein regulates cell size in mammals, said Wu. The scientists next used antibodies to mark specific types of brain cells. Those experiments showed that the neural stem cells in the mutant mice developed into the normal lineages of cells in the embryonic brain. Additional cell-labeling studies indicated that the increase in brain cells likely resulted both from increased proliferation of cells and reduced programmed cell death.

Wu and her colleagues also used “neurosphere” cell cultures of stem cells from the brains of both normal and mutant mice to explore in detail how the stem cells developed. Neurospheres are tiny aggregates of brain cells that include stem cells and their progeny at different stages of development. By applying growth factors, the neurospheres of cells from different brain areas can be induced to proliferate and differentiate.

“We found that mutant neurospheres proliferated more readily than normal neurospheres,” said Wu. “As in the *in vivo* studies, we found that the mutant neurospheres, like the normal neurospheres, produced the normal range of neural cells – neurons, astrocytes and oligodendrocytes. We conclude that these experiments suggest that the PTEN protein is a major modulator in neural stem cells of the proliferative cell cycle and of programmed cell death,” she said.

While Wu emphasized that it is still relatively early, it may be that “the signaling pathway elucidated by this study will have an impact on future clinical studies aimed at manipulating stem cell populations,” she said. Also, she said, establishing PTEN’s role in regulating neuronal stem cell development should lead to better understanding of how mutations that abolish PTEN function allow unchecked cell proliferation in cancers.

Wu and her colleagues plan further studies to explore whether PTEN serves as a switch that triggers normally quiescent stem cells to enter the cell cycle and proliferate. They also plan to analyze in detail how knocking out PTEN in adult animals triggers cancers. Such understanding could lead to drug therapies that would prevent hyperactivation of the PTEN-controlled pathway, to treat such cancers.