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Well-known enzyme is unexpected contributor to brain growth

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An enzyme researchers have studied for years because of its potential connections to cancer, diabetes, heart disease, hypertension and stroke, appears to have yet another major role to play: helping create and maintain the brain.

When scientists at Washington University School of Medicine in St. Louis selectively disabled the enzyme AMP-activated protein kinase (AMPK) in mouse embryos, overall brain size was reduced by 50 percent, the cerebrum and cerebellum were shrunken, and the mice died within three weeks of birth.

Researchers showed that the version of AMPK they disabled was essential to the survival of neural stem cells that create the central nervous system. Many scientists believe these same cells also regularly produce new brain cells essential for learning and memory and the general upkeep of the adult brain.

"For years, scientists have showed how AMPK regulates multiple metabolic processes, and revealed how that influence can affect cancer, diabetes, and many other diseases," says senior author Jeffrey Milbrandt, M.D., Ph.D., the David Clayson Professor of Neurology. "Now, for the first time, we've shown that AMPK can cause lasting changes in cell development. That's very exciting because it opens the possibility of modifying AMPK activity to improve brain function and health."

The study was the featured paper in the February issue of *Developmental*

Cell.

AMPK regulates the energy usage of cells and becomes active when energy resources are low, such as during exercise or times of dietary restriction. Activated AMPK inhibits processes that consume energy, like protein synthesis or fatty acid synthesis, and promotes processes that produce energy, such as the oxidation of fatty acids, the uptake of the sugar glucose, or the creation of mitochondria, which are cellular energy-making units. Activated AMPK also suppresses cell reproduction, an ability that scientists have shown can help shut down the proliferation of some cancer cell lines.

The AMPK enzyme is composed of three subunits called alpha, beta and gamma. The human genome contains genes for two to three versions of each subunit. Until now, the beta unit seemed to be "a boring linker" that merely held the three subunits together, according to Milbrandt.

Instead, Milbrandt and Dasgupta found that the beta subunit was determining where AMPK did its job. AMPK with one version of the subunit, beta 1, was found both in the nucleus of cells and in the body of the cell, which is called the cytoplasm. AMPK with beta 2 was never found in the nucleus—just the cytoplasm.

They showed that when activated AMPK gets into the nucleus of stem cells, it inactivates the retinoblastoma protein, a master regulator of cell reproduction. This allows neural stem cells to survive and proliferate.

"Inhibiting AMPK is something that most cells don't like. It can lead to a variety of consequences, including cell death, but many cell types can tolerate it," says lead author Biplab Dasgupta, Ph.D., research instructor in pathology and immunology. "In contrast, neural stem cells undergo catastrophic cell death in the absence of AMPK containing the beta 1 subunit. We also suspect loss of this form of AMPK may cause severe

problems for other stem cells."

Dasgupta calls the new finding particularly interesting given previous connections between AMPK and exercise.

"Exercise activates AMPK and improves cognitive function," says Dasgupta. "Our results suggest brain function may improve because additional activated AMPK makes it easier for adult neural stem cells to reproduce and become new brain cells."

Retinoblastoma, the protein regulated by AMPK in the nucleus, also has less well-defined influence on the ability of stem cells to take on specialized characteristics, and this has Milbrandt intrigued about possible connections between AMPK's new role in stem cells and the long-term health effects of malnutrition during pregnancy. A 1977 study of children born to women starved by the Nazis during World War II suggested that the children had increased risk of heart disease, diabetes, stroke and hypertension.

While these are some of the same disorders that have been linked to AMPK activity in adults, those previous links were made through AMPK's role as a manager of cellular energy usage. Milbrandt wonders if changes in AMPK activity triggered by malnutrition could also be affecting stem cell activity in ways that increase long-term health risks in developing infants.

AMPK's role reversal in stem cells calls for careful use of the enzyme in cancer therapy, the researchers note. Recent studies have shown that stem cells can become cancerous, and in those cancers the researchers now believe it might be better to inhibit AMPK than to activate it. Dasgupta will test this hypothesis on cancer stem cell lines.

Milbrandt plans to learn more about how production of different forms

of AMPK is regulated.

"Manipulating this regulation may enable us encourage the development of new brain cells," he says. "We might use that not only to treat medical conditions where brain development is hampered but also to improve cognitive function generally."

More information: Dasgupta B and Milbrandt J. AMP-activated protein kinas phsophorylates retinoblastoma protein to control mammalian brain development. *Developmental Cell*, February 2009.

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