Newly discovered protein makes sure brain development isn't 'botched'

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(Medical Xpress) -- Johns Hopkins scientists have discovered a protein that appears to play an important regulatory role in deciding whether stem cells differentiate into the cells that make up the brain, as well as countless other tissues. This finding, published in the April *Developmental Cell*, could eventually shed light on developmental disorders as well as a variety of conditions that involve the generation of new neurons into adulthood, including depression, stroke, and posttraumatic stress disorder.

Researchers have long known that a small group of proteins called Notch plays a pivotal role in helping the immature cells present in embryos to develop into the variety of cells present throughout the body, including those that make up the brain, blood, kidneys and muscles.

“Notch signaling is involved in almost all aspects of tissue development,” explains study leader Valina Dawson, Ph.D., a professor in the departments of Neurology, Neuroscience, and Physiology and co-director of the Stem Cell and Neuroregeneration Programs at the Institute for Cell Engineering at the Johns Hopkins University School of Medicine.

However, she says, even for researchers who have been studying Notch for decades, how this small group of proteins manages the development of such a diverse array of tissues and organs in the body remains unknown. It’s a pivotal mystery to solve, Dawson adds, since problems in Notch signaling seem to be involved in various cancers, Alzheimer’s

disease, juvenile stroke and many other health problems.

In their new study, Dawson and her colleagues shed light on one way Notch proteins might be regulated, through a protein they recently discovered in the lab. This protein seemed to be involved in development, but at first, the researchers didn't know its function.

To determine what purpose this protein serves in cells, Dawson, postdoctoral fellow Zhikai Chi, M.D., Ph.D., and their colleagues started by trying to determine what other proteins it's able to bind to. By adding the mystery protein to cell cultures that expressed a variety of other proteins, they determined that the unknown protein altered cellular activity in those expressing Notch.

Since Notch is involved intimately in determining the fate of brain precursor cells, driving neural stem cells to proliferate and determining whether they become neurons or supporting cells known as glia, the researchers next examined how this mystery protein affected brain development in mouse embryos. They found that by increasing expression of the unknown protein, more neurons developed in certain parts of the developing brain, including the intermediate zone and cortical plate. In contrast, decreasing expression led to fewer neurons. Taken together, Dawson says, these experiments provided even more evidence that their unknown protein was somehow influencing Notch.

To determine exactly how the mystery protein was affecting Notch, the researchers examined the effect of the protein on neural stem cells in the process of differentiating into mature cell types. Increasing the amount of the unknown protein swayed development as if Notch wasn't working. Since the unknown protein appeared to prevent Notch from acting on cells, the researchers named it Botch for "blocks Notch."

With Botch's role now clear, the researchers turned next to the

mechanism behind how this protein exerts its influence. A series of experiments suggests that Botch interacts with Notch in the Golgi body, a cellular organelle involved in modifying proteins. For Notch to act in development, an immature version of this protein needs to be cleaved in order for the protein to be rearranged. Botch appears to prevent this pivotal modification from taking place, reducing the amount of mature Notch available to do its job.

Because Botch appears to play such an important role in regulating Notch, Dawson says, it could be involved in a number of diseases in which the generation of new neurons is misregulated. She and her colleagues are already performing some preliminary experiments to determine whether Botch expression might vary from the norm in diseases such as depression, which has been linked to a decrease in neurogenesis in the brain's hippocampus. Eventually, researchers might be able to develop drugs that act on Botch to restart stalled neurogenesis, potentially treating depression and other diseases in which a lack of neurogenesis is thought to play a role.

"There are potentially some very large neurological problems that could be addressed through changing Botch activity," Dawson says.

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