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Growing up as a neural stem cell: The importance of clinging together and then letting go

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Can one feel too attached? Does one need to let go to mature? Neural stem cells have this problem, too.

As immature cells, neural stem cells must stick together in a protected environment called a niche in order to divide so they can make all of the cells that populate the nervous system. But when it's time to mature, or differentiate, the neural stem cells must stop dividing, detach from their neighbors and migrate to where they are needed to form the circuits necessary for humans to think, feel and interact with the world.

Now, stem cell researchers at UCLA have identified new components of the genetic pathway that controls the adhesive properties and proliferation of neural stem cells and the formation of neurons in early development.

The finding by scientists at the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA could be important because errors in this pathway can lead to a variety of birth defects that affect the structure of the nervous system, as well as more subtle changes that impair cognitive and motor functions associated with disorders such as autism.

The results of the four-year study are published April 26, 2012 in the peer-reviewed journal *Neuron*.

The UCLA team found that a delicate balance of gene expression enables the pool of neural stem and progenitor cells in early development to initially increase and then quickly stop dividing to form neurons at defined times.

"One of the greatest mysteries in developmental biology is what constitutes the switch between stem cell proliferation and differentiation. In our studies of the formation of motor neurons, the cells that are essential for movement, we were able to uncover what controls the early expansion of neural stem and progenitor cells, and more importantly what stops their proliferation when there are enough precursors built up," said Bennett G. Novitch, an assistant professor of neurobiology, a Broad Stem Cell Research Center scientist and senior author of the study. "If the neurons don't form at the proper time, it could lead to deficits in their numbers and to catastrophic, potentially fatal neurological defects."

During the first trimester of development, the neural stem and progenitor cells form a niche, or safe zone, within the nervous system. The neural stem and precursor cells adhere to each other in a way that allows them to expand their numbers and keep from differentiating. A protein called N-cadherin facilitates this adhesion, Novitch said.

When it is time for the neural precursors to become motor neurons, two proteins that repress gene expression, called Foxp2 and Foxp4, become elevated and then silence N-cadherin expression, causing the clustered neural stem and precursor cells to break apart and begin differentiating.

"We have these cells in a dividing state, making more of themselves, and to make neurons that process has to be stopped and those contacts between the cells disassembled," Novitch said. "Until now, it has not been clear how the cells are pulled apart."

Novitch and his team showed that if you eliminate Foxp protein function, motor neurons and other mature cells in the nervous system are not properly formed because the N-cadherin gene is not silenced, confirming the delicate balancing act that must be achieved for normal development of both the stem and precursor cells and their neuronal progeny.

"It's a fundamental discovery. Most studies have focused on defining what promotes the adhesiveness and self-renewal of neural stem cells, rather than what breaks these contacts," Novitch said. "We were also surprised to see how small changes in the degree of cell adhesion can markedly alter the development and structure of the nervous system. It's all about balance, if you have too many or too few stem and precursor cells, the result could be disastrous."

Going forward, Novitch and his team will examine whether the functions of Foxp2 and Foxp4 in regulating cell adhesion may be important for the maintenance and differentiation of neural stem cells in the adult brain, and whether the loss of their activity may contribute to the formation and growth of brain tumors. In addition, Novitch's group plans to examine whether their findings are relevant for investigating the function of Foxp2 and Foxp4 in other aspects of neural development, as mutations in Foxp proteins have previously been associated with a range of intellectual disabilities and speech-language disorders.

"It is tempting to speculate that these loss-of-function phenotypes might result from abnormal cell adhesion associated with dysregulated N-cadherin expression or function," the study states. "If true, these findings could provide a molecular explanation for the association of Foxp mutations with developmental human language and motor disorders, including autism."

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