New study pinpoints gene controlling number of brain cells (w/ Video)

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In populating the growing brain, neural stem cells must strike a delicate balance between two key processes - proliferation, in which the cells multiply to provide plenty of starting materials - and differentiation, in which those materials evolve into functioning neurons.

If the stem cells proliferate too much, they could grow out of control and produce a tumor. If they proliferate too little, there may not be enough cells to become the billions of neurons of the brain. Researchers at the University of North Carolina at Chapel Hill School of Medicine have now found that this critical balance rests in large part on a single gene, called GSK-3.

The finding suggests that GSK-3 controls the signals that determine how many neurons actually end up composing the brain. It also has important implications for patients with neuropsychiatric illness, as links have recently been drawn between GSK-3 and schizophrenia, depression and bipolar disorder.

One of the genes associated with schizophrenia appears to use GSK-3 as an intermediary to exert its effects on nerve cells. In addition, lithium, a popular treatment for bipolar disorder, acts, in part, by shutting down GSK-3. "I don't believe anyone would have imagined that deleting GSK-3 would have such dramatic effects on neural stem cells," said senior study author William D. Snider, M.D., professor of neurology and cell and molecular physiology, and director of the UNC Neuroscience Center. "People will have to think carefully about whether giving a drug

like lithium to children could have negative effects on the underlying structure of the nervous system."

In a study appearing online Sunday October 4th in the journal Nature Neuroscience, Snider and his colleagues created a mouse model in which both forms of the GSK-3 gene - designated alpha and beta - had been deleted. They decided to go after GSK-3 - which stands for glycogen synthase kinase 3 - because it is one of the most studied kinases or signaling molecules in all of biology.

The researchers used a "conditional knock-out" strategy to remove GSK-3 at a specific time in the development of the mouse embryo, when a type of cell called a radial progenitor cell had just been formed.

As the brain develops, neural stem cells evolve through three different stages -- neural epithelial cells, radial progenitor cells and intermediate neural precursors. The radial progenitor cells are especially important because they are thought to provide the majority of the neurons of the developing brain but also differentiate themselves to give rise to all the cellular elements of the brain. The researchers discovered that deleting GSK-3 during this second phase of development caused the radial progenitor cells to be locked in a constant state of proliferation.

"It was really quite striking," said Snider. "Without GSK-3, these neural stem cells just keep dividing and dividing and dividing. The entire developing brain fills up with these neural stem cells that never turn into mature neurons."

GSK-3 is known to coordinate signals for proliferation and differentiation within nerve cells through multiple "signaling pathways." Thus, the researchers looked to see what effect deleting the molecule had on some of these pathways. They found that every one of the pathways that they studied went awry.

Snider and his colleagues now want to see if adding GSK-3 back to their genetically engineered mice can convert the proliferating stem cells into neurons, possibly resulting in three to four times as many neurons in the mutants as normal.

"I find that quite interesting because I can't think of any other manipulation that potentially would enable you to simply dial up and down the number of neurons that are generated in the brain," said Snider.

Source: University of North Carolina School of Medicine (news : web)