The birth of neurons, called neurogenesis, is known to continue throughout life in some areas of the brain. Research continues to show that the process is one of the brain's methods of self-repair that could be harnessed for therapeutic purposes; abnormal neurogenesis may contribute to some disorders and may provide new avenues for therapy. So too do the immature and versatile cells known as stem cells continue to show promise as treatments. Researchers made progress in 2006 in unraveling the pathways through which stem cells develop into neurons. But can stem cells take on specific jobs in the brain?

Neurogenesis in the Cortex

Neurogenesis has been known since 1998 to occur in the hippocampus of the adult human brain. Less clear is whether new neurons are produced in other areas, and whether the brain's remarkable adaptability, or plasticity, results from the remodeling of existing cells or the production of new ones.

An innovative method for dating brain cells is the use of radiocarbon (14C), which was released in massive amounts during aboveground nuclear testing in the 1950s and has declined measurably ever since, taken up by the earth's atmosphere and into the DNA of plants, animals, and humans. In 2005 a team led by Jonas Frisen of the Karolinska Institute in Stockholm used 14C dating to establish that in the cortex of adult humans, 14C levels matched those in the atmosphere at the time of the individual's birth—suggesting that few, if any, cortical neurons had been produced later in life.

Frisen and colleagues teamed up with several other laboratories for a more extensive study, reported in Proceedings of the National Academy of Sciences.[1] Working with autopsied brain tissue from seven individuals born between 1933 and 1973, the investigators measured neurons from all lobes of the cortex. They again found 14C levels corresponding to those at the time of each subject's birth, providing strong evidence that neurogenesis in the cortex is limited to the developing brain.

They surmise that although neurogenesis in the hippocampus may play a role in some types of memory, cognitive functions such as learning and analysis are handled by cortical cells that have been in place since birth, and that in the cortex stability is favored over plasticity.

The cortex is the seat of "higher" functions such as reason and analysis and is considered the part of the brain that distinguishes humans from other species. A study reported in Nature Neuroscience shows that cortical neurons may be some of the first cells produced as the human embryo takes form.

Researchers led by Colin Blakemore of the University of Oxford and Pasko Rakic of Yale University identified a distinctive population of neurons emerging within the first few weeks of pregnancy. These predecessor cells begin life in the area that becomes the cortex, appearing before other neurons that are produced deeper in the brain, and migrate to positions in the cortex as the brain develops.

The predecessors also produce a different set of marker proteins, suggesting that they are a unique cell population. The finding provides evidence that the first cells of the distinctly "human" brain are present at a very early stage in embryonic development, and it is important for understanding the development of the normal brain and, possibly, many cognitive disorders.[2] For example, the recent findings in autism suggest abnormalities in cortical development in that disorder.

The therapeutic use of stem cells depends on their ability to develop into specific cell types needed to correct a given illness by performing a specific function. According to a report in Nature Neuroscience, this plasticity, or "pluripotency," has its limits.[3]

Researchers led by Sally Temple of Albany Medical College in New York found that the timing that governs cortical development is encoded within the progenitor cells that give rise to the neurons—not signaled by factors

in the neurons' environment. The cortex develops in layers, with neurons for each layer produced according to a predictable schedule.

The investigators found that when neural progenitor cells taken from mice were cultured in isolation, the resulting neurons appeared in the same sequence as they would in the embryonic brain. At each stage the cells lost some of their plasticity. By reducing a gene called Foxg1, required for cortical development, the investigators were able to reset the timing of mid-gestation but not late-gestation neurons.

The finding has important implications for stem cell therapy, suggesting that the sequence of development is programmed right from the beginning and that the cells can be diverted from their "fate" only during a narrow window of time.

A Natural Response to Injury

Many studies in animals have shown that the adult brain can respond to injury or "insult" with a surge of neurogenesis—an ability that could be exploited to treat injury from trauma or stroke if the precise steps were understood. Reporting in the Journal of Neuroscience, T. Yamashita and colleagues found that, after a stroke, a group of neural stem cells that normally produces only olfactory cells is able to produce new neurons in the striatum where the injury occurred.4

These new neurons proved able to form connections with neighboring striatal cells. The finding has implications for treating stroke and other neurological disorders.

To study the role of neurogenesis in stroke recovery in humans, David Greenberg of the Buck Institute for Age Research and his research group looked for newborn neurons in human brain biopsies taken from stroke-induced brain lesions. As reported in Proceedings of the National Academy of Sciences, the areas around the site of injury showed molecular markers of newborn neurons—especially near blood vessels, which produce growth factors that enhance division and growth of neurons during neurogenesis.[5] The finding suggests that some neurogenesis takes place and that medications to enhance the process could be useful treatments.

Neurogenesis may also be a natural response to spinal cord injury, one that could be harnessed for therapeutic purposes. In the Journal of Neuroscience, Michael Tuszynski and Fred Gage of the Salk Institute and colleagues reported their finding that adult rhesus monkeys given an experimental spinal cord injury showed an increase of more than 80-fold in the number of newly divided cells.[6] By seven months after the injury, many of the cells had become various types of support cells; some were producing myelin, the fatty insulation crucial to the axons of injured neurons. The work is evidence that some neurogenesis takes place to help repair spinal cord injuries, and it could be enhanced by the right therapies.

Neurogenesis and Epilepsy

Some animal studies show that epileptic seizures stimulate neurogenesis. However, a study reported in a special neurogenesis issue of the journal Hippocampus shows that the newly born cells grow not into replacement neurons but into glia (cells that perform "support" functions, such as producing myelin, rather than transmit signals).[7] Jack Parent of the University of Michigan Medical Center and his team found that rats experiencing chemically induced seizures showed a marked increase in brain cells, as indicated by a chemical that fastens onto dividing cells, for a two-week observation period after the procedure.

Because the cells developed into glia, unlike the newborn neurons that follow stroke-induced injury, the study raises an important question: Why does the brain produce different cell types in response to different injuries? Further research will shed light on neurogenesis as a means for repair and may point toward new treatments for epilepsy.

Another team led by Parent has found that neurogenesis after a seizure may be part of the problem. In human and experimental temporal lobe epilepsy, for example, a part of the hippocampus called the dentate granule layer is often abnormal. The investigators reported in the Annals of Neurology that in rats with prolonged seizures, progenitor cells in this layer area migrate and develop abnormally.[8] Although neurogenesis persists throughout life in some areas of the hippocampus, the researchers surmise that seizures disrupt the neurons' migration, leading to faulty integration of newborn cells and possibly to recurrent seizures.

Antidepressants Boost Neurogenesis at Specific Stage

Antidepressants are suspected to increase the rate of neurogenesis in the hippocampus. But the medications currently available take three to four weeks before improving the mood of patients with depression, and about a third of patients do not respond to treatment at all. Many studies suggest that drugs such as Prozac may ultimately work by increasing the rate of neurogenesis; if the steps involved were better understood, medications could be developed to stimulate neurogenesis more directly.

In Proceedings of the National Academy of Sciences, researchers at Cold Spring Harbor Laboratories reported having developed a strain of "reporter" mice with a blue fluorescent protein in the nuclei of cells derived from neural precursors.[9] By checking the "blue" neurons for various marker proteins, then exposing the cells to fluoxetine (Prozac), the team ascertained that stem cells at one specific stage of development are the drug's sole target. Finding more direct ways of boosting this population of cells might result in treatments for depression that work more quickly and effectively.

Disease Proteins and Brain Cell Development

Prion protein is best known for its role in causing disease: when misfolded, it is the culprit in brain encephalopathies, such as mad cow disease and its human counterpart, Creutzfeldt-Jakob disease. But studies in recent years have revealed that prion proteins are not abnormal by definition; rather, they are converted into a disease-producing form as they unfold and refold, and it is the amount of misfolded prions that determines whether or not a disease develops. Less is known about the normal prion protein's role in brain function.

Jeffrey Macklis of Harvard University, Susan Lindquist of the Massachusetts Institute of Technology, and colleagues have shown that the prion protein is plentiful in areas of the brain where neurogenesis takes place. In the study, published in Proceedings of the National Academy of Sciences, levels of prion protein were closely linked with the rate at which precursor cells differentiated into neurons; experimental mice that overproduced the protein had more proliferating brain cells than normal or knockout mice.[10] Further studies will shed light on this protein's role in the normal brain and may result in new approaches to prevent and treat prion diseases.

As reported in Stem Cells Development, researchers led by Kiminobu Sugaya at the University of Central Florida showed that excessive levels of amyloid precursor protein, such as are found in Alzheimer's disease, may block the production of new neurons by diverting stem cells to become astrocytes.[11] Stimulating cultured human neural stem cells with this protein increased their differentiation into astrocytes, while blocking the protein with an antibody prevented this differentiation.

In transgenic mice developed to produce beta-amyloid, transplanted human stem cells differentiated into glia rather than neurons. The results suggest that high levels of amyloid precursor protein may thwart the brain's self-healing efforts by changing the course of cells that would otherwise have grown into replacement neurons—a role that will have to be better understood if stem cells are to be a therapy for Alzheimer's disease and other conditions.

Support Cells Turn Cancerous

The same process that determines which neural stem cells become neurons and which become support cells may explain another, more ominous observation: stem cells also have the capacity to develop into tumors. As reported in Neuron, a group led by Arturo Alvarez-Buylla of the University of California at San Francisco identified

a group of neural stem cells carrying a receptor for a growth factor.[12] An infusion of this growth factor stimulated these cells to grow excessively and show some features of tumors (see also Nervous System Injuries).

Meanwhile, Patricia Casaccia-Bonnefil of the Robert Wood Johnson Medical School and her fellow researchers reported in the Journal of Neuroscience that glia may become cancerous through lack of apoptosis, or programmed cell death.[13] The researchers studied knockout mice missing the apoptosis-initiating p53 gene.

The absence of p53 did not automatically result in cancer. But, when the mice were given an experimental cancer-causing stimulus, their neural stem cells showed dramatic changes consistent with cancer—dividing more rapidly, for example, and not fully differentiating.

Notch Protein Activates Stem Cells

The ultimate goal of stem cell therapy is to activate "endogenous" stem cells—those existing in the patient's own body. In Nature, Ronald McKay of the National Institute of Neurological Disorders and Stroke reported on a model of stem cell expansion that may help realize this goal.[14]

Activation of a receptor known as Notch induces a chain of events that promotes the survival of neural stem cells. When adult rats were treated with a molecule that locks into the Notch receptor, they showed increased numbers of progenitor cells and improved motor skills after an experimental stroke injury. The work suggests a method for stem cell expansion both in culture and in a host animal receiving transplants, possibly even turning stem cells back on.

The stem cell field continues to flourish but the studies above indicate how much we still do not know. Directing the development of stem cells to become specific cell types (nerve cells, or glia) and not to become cancer cells remains the big challenge.

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