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Take comfort in human neurogenesis

Even as children, most of us will have come across the well-rehearsed dogma that our brain cannot replace dying neurons. And as students returning from basic neuroscience classes, we may even have lain awake some nights mulling over the consequences of the inevitable, gradual loss of our precious and predetermined 100 billion neuronal quota. Sleep easy. On page 1313 of this issue, Fred Gage and colleagues in La Jolla and Göteburg report that the adult human brain is capable of neurogenesis.

Most cells are continually dividing, repairing and replenishing organs and other systems. In the developing embryo, cells have a truly prodigious capacity to replicate and neural precursors are no exception. So where did this belief in irreplaceable adult brain cells come from? In the broadest sense, neurons are thought of as unusually large and complicated cells that are highly differentiated. Intuitively, therefore, it seems unlikely that such cells could easily de-differentiate and replicate. In fact, recent work suggests that adult neurogenesis comes from endogenous stem-like cells that persist in the brain, bypassing the need for de-differentiation

Many studies over the last few decades have chipped away at the 'non-diving adult brain cell' edifice. As early as the 1960s, Altman and Das provided good evidence for neurogenesis in the adult rat hippocampus, and in 1967 the same authors, moved beyond 'evidence' and presented a paper simply entitled "Postnatal neurogenesis in the guinea-pig." (The choice of guinea-pig was not trivial as, unlike mice and rats, they are born with relatively mature brains that undergo very little structural change after birth.) Given this precedent, surely humans could match rats and guinea-pigs in regenerative brain capacity. Not so, said the critics, for the simple reason that rodents do not belong to the elite 'higher' animals club. An influential 1985 article by Pasco Rakic (in which he reported an absence of neurogenesis in rhesus monkeys) argued that perhaps neuronal replication could not be tolerated in primates because it might interfere with learning and memory.

Earlier this year, Gould and colleagues made the jump to primates, showing that adult marmosets can generate new dentate gyrus neurons (and went on to show that proliferation of these neurons can be diminished by stress). But this was just marmosets—long-tailed, small American monkeys, not even old-world, and far short of the apes that are more closely related to humans—and many naysayers stuck to the 'no higher primate neurogenesis' line. For higher primates, so the theory went, evolution has favored a stable brain that rules out any tampering with important hard wiring, over regenerative capacity. Apparently not so.

Fred Gage and colleagues took advantage of a rare opportunity to look for new neurons in the dentate gyrus of humans. Bromodeoxyuridine is a thymidine analog and as such is incorporated into the newly synthesized DNA of dividing cells. Once incorporated, it can be detected readily using standard immunohistochemistry. It is occasionally administered to cancer patients to check for tumor cell proliferation and Gage and colleagues mused that because the BrdU would also label new neurons, they could examine the brains of such patients for signs of neurogenesis. They arranged to receive hippocampal post mortem tissue from five squamous-cell carcinoma patients who had each received a single intravenous infusion of 250 mg of BrdU and died between 16 and 781 days later. In all five samples, BrdU-labeled cells were found in the granule cell layer of the dentate gyrus. Simultaneous labeling with neuronal markers, and confocal microscopy confirmed that these new cells were neurons.

Now that human neurogenesis is apodictic, how does this change our view of the brain? For one, it forces a new look at plasticity for an organ previously considered an anatomical *fait accompli* at birth. The idea of neuroplasticity has included processes by which new synapses can be formed and existing synapses strengthened, but until now has excluded any significant contribution from completely new cells entering pathways. Neurogenesis also opens the possibility of autologous repair and regeneration. Recently there has been much interest in cell transplantation and other protocols designed to slow and even reverse the neurodegeneration of disorders such a Parkinson disease, Huntington chorea and Alzheimer disease, all of which share a gradual loss of certain categories of neurons. These losses might reflect not only the insult that causes the neurons to die, but a failure of an otherwise expected regeneration that ordinarily repairs the loss. A better understanding of natural neurogenesis, its relation to aging and the factors that stimulate it and limit it will be important if cell replacement is to take its place in the clinic.

Of course, the rate of neuronal proliferation is not high (Gage estimates that in the adult mouse hippocampus, for example, there might be in the order of 500 new neurons per day), and interpretation of the impact of neurogenesis assumes that the newly created neurons are functional. This will not be straightforward to establish. As mentioned above, Gould *et al*. reported recently that in marmosets, neurogenesis is diminished under stress, and Gage and colleagues have shown the opposite—that an enriched environment can increase neurogenesis in mice. That neurogenesis responds to environmental cues suggests a functional link, but there is much work to be done to establish function. But such difficulties and challenges do not detract from what might be a uniquely human response to the demonstration of human adult neurogenesis—it's just nice to know it's there!