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New Findings Change Understanding of Adult Stem Cells

Researchers have found neural stem cells in the peripheral nervous system of adult animals, where they were not believed to exist. The studies show that the intrinsic properties of neural stem cells vary according to the region of the peripheral nervous system in which the cells are located.

Taken together, these findings, which were published in two articles in the August 15, 2002, issue of the journal *Neuron*, suggest that successful application of stem cells to regenerate damaged peripheral nervous system (PNS) tissue will require that researchers match the origin of the stem cell to the specific tissue they are trying to repair.

Stem cells are immature progenitor cells that give rise to more specialized cells that form tissues and organs. Neural stem cells give rise to the nervous system. Although great progress has been made in understanding the properties of stem cells, we are just beginning to understand how those functions are regulated, said Howard Hughes Medical Institute investigator Sean J. Morrison, who is at the University of Michigan.

Morrison and his colleagues have been studying stem cell biology in the context of neural development and blood cell development. The studies published in *Neuron* focused on neural crest stem cells (NCSCs), which were so-named because during embryonic development, they migrate out of the neural tube and give rise to a number of different tissues including the peripheral nervous system.

Morrison and his colleagues decided to search for NCSCs in adult animals because their studies of rat embryos were revealing that the cells were present much later in development than they thought possible. The idea that these cells would be found in the peripheral nervous system ran counter to prevailing opinions, said Morrison.

"Previous work on the peripheral nervous system suggested that neural crest stem cells differentiated during fetal development," he said. "People firmly believed that there would be no neural crest stem cells in the adult peripheral nervous system. It had been known for quite a while, however, that there are stem cells in the adult central nervous system. But the CNS was thought to be a more dynamic environment where stem cells and neurogenesis could persist throughout adult life, at least in certain locations.

Forging ahead, Morrisons group isolated NCSCs from the gut tissue of adult rats, cultured those cells and then introduced them into chick nerves to explore properties of the NCSCs. These studies showed that the NCSCs were self-renewing and multipotent, meaning they were able to differentiate into both neurons and supporting glial cells. These adult cells had most of the properties of embryonic NCSCs, but they were unable to become serotonergic and noradrenergic neurons, two cell types that embryonic NCSCs are capable of becoming.

"This finding was significant because some people assumed that adult stem cells would have the same properties as fetal stem cells," said Morrison. "But work on blood-forming stem cells suggested just the opposite — that while the adult stem cells are self-renewing and multipotent, they do change their properties in certain ways. They lose the ability to make certain subtypes of cells that are made only during fetal development. And in the PNS, serotonergic neurons and noradrenergic neurons are only made during fetal development, suggesting that NCSCs undergo changes perinatally that are analogous to those in blood-forming stem cells."

According to Morrison, much work remains to fully understand adult stem cells and whether they might one day have clinical applications. "We don't know yet whether these cells exist in humans," he said. "And we don't know what they normally do in the gut. But these findings offer the possibility that there could be stem cells that can engage in repair of the PNS, without requiring exogenous cells to be transplanted. That opens up a new spectrum of therapeutic opportunities that we didn't even think were on the table."

In a related set of experiments, Morrison and his colleagues isolated NCSCs from the gut and sciatic nerve of rat embryos. They then tested how the cells from these two different tissues responded to various regulatory signals, in an attempt to reveal whether there were intrinsic differences in the cells.

"In the past, people have argued that distinct regions of the nervous system were different because they were in different environments," said Morrison. "And people have gone to the point of arguing that there might be a single type of neural stem cell within the CNS, as though the stem cell itself was a blank slate."

Morrison and his colleagues developed a technique that enabled them to compare the newly isolated cells at the same point in development and before they had been cultured. This technique allowed them to study the cells before they were exposed to chemicals in the cell culture that might erase the intrinsic properties of the cells.

Their studies revealed intrinsic differences in the two types of NCSCs. Gut NCSCs were more responsive to chemical signals that caused differentiation into neurons, and sciatic nerve NCSCs were more responsive to signals that produced glial cells. When the researchers transplanted the cells into developing chick nerves, the gut NCSCs made only neurons and the sciatic nerve cells produced only glial cells.

According to Morrison, the emerging theory is that stem cells rely on a combination of intrinsic properties and environmental signals to develop into the diverse populations of adult cells observed in the nervous system.

"The clinical implications of these findings could be important," he said.

"People attempting to use neural stem cells therapeutically have tended to think that any stem cell that makes a neuron will do, and that you only need to get the culture conditions right. But our finding that stem cells from different regions of the peripheral nervous system have intrinsic differences in their ability to respond to factors, and their ability to make different types of cells, suggests that its really important to match the origin of the stem cell to the therapeutic job that youre trying to do."

The team in the Morrison laboratory that performed these studies was led by graduate student Genevieve Kruger and Research Assistant Suzanne Bixby, and included graduate student Nancy Joseph and postdoctoral fellows Jack Mosher and Toshihide Iwashita.