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Brain cell migration during normal development may offer insight on how cancer cells spread

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By shedding new light on how cells migrate in the developing brain, researchers at Fred Hutchinson Cancer Research Center also may have found a new mechanism by which other types of cells, including cancer cells, travel within the body. The findings by Jonathan Cooper, Ph.D., member and director of the Hutchinson Center's Basic Sciences Division, and Yves Jossin, Ph.D., a research fellow in Cooper's laboratory, published online April 24 in *Nature Neuroscience*, could lead to a better understanding of neurological development and, possibly, cancer metastasis.

During normal development cells divide, arrange themselves in appropriate patterns, and specialize to form discrete tissues and organs. For the body to develop properly, cells must coordinate their migratory patterns and the process by which they differentiate, or evolve from less-specialized cells into more-specialized cell types. A lack of such coordination leads to disordered development and, in some cases, cancer.

Jossin and Cooper set out to analyze how cells migrate in the cerebral cortex of the developing brain. The cerebral cortex, gray matter of the cerebrum, is the brain's command and control center where cognition and planning occur, and it is particularly well developed in humans.

The cerebral cortex is composed of horizontal layers of nerve cells, or neurons, which are specialized for different functions and connected

vertically into circuits. If some neurons are in the wrong layers, the wiring can be defective and neurological disorders including epilepsy, autism and schizophrenia may result.

In the fetus, the cortex grows "from the inside out" via the sequential addition of new neurons, which move from the inside, pass between neurons in previously established intermediate layers, and form new layers on the outside. How the migrations are regulated remains unclear despite years of study.

Jossin and Cooper now report the discovery of signals that control a particular stage in a cortical neuron's journey. New neurons initially move in a straight line, from the inside to the outside, until they reach a layer called the intermediate zone. This zone contains relatively few neurons but many connecting fibers, or axons. When new neurons reach this layer, they lose their way and start wandering – up, down, left and right, frequently changing direction. When, seemingly by chance, they emerge from the intermediate zone, they realign with their original direction of movement and speed ahead through layers of differentiated neurons towards the outer surface of the cortex.

The researchers aimed to determine how neurons get back on track after they emerge from the chaos of the intermediate zone. They identified a signaling protein, called Reelin, which is made by cells in the outermost layer of the cortex. It has been known for years that mutations in the Reelin gene cause profound cortical layering abnormalities in rodents and people, but it has been unclear which stage of neuron migration goes awry when Reelin is absent.

The new study shows that new neurons respond to Reelin as they emerge from the intermediate zone. "This is remarkable because the top layer of the cortex, where Reelin is made, is widely separated from the top of the intermediate zone, where it acts, so the Reelin protein must be diffuse,"

Cooper said. "It is also remarkable that Reelin seems not to be a direction signal itself. Rather, Reelin triggers changes in the membranes of the migrating neurons that allow the cells to respond to direction signals."

The researchers show that a membrane protein called N-cadherin increases on the surface of neurons when the neurons encounter Reelin. The surface increase in N-cadherin allows the cell to choose the appropriate direction for its next stage of migration. "This represents a new and surprising function for N-cadherin," Jossin said, "because normally this protein acts as a cellular stabilizer and not as an orchestrator of migration."

For example, elsewhere in the cortex, N-cadherin forms tight adhesions between adjacent cells and prevents them from moving. Indeed, the general role for cadherins in the body is to stabilize sheets of cells and organize tissues by holding cells together.

"The new role for N-cadherin in orienting migrating cells is quite unexpected and suggests that cadherins on the surface of other types of normal or cancer cells may also be involved in helping them move rather than stay in place," Jossin said. "This finding could provide new clues to how normal and cancerous cells migrate within the body," he said.

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