Neural stem cell study reveals mechanism that may play role in cancer

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In the dynamic world of the developing brain, neural stem cells give rise to neurons deep within the brain's fluid-filled ventricles. These newborn neurons then migrate along the stem cell fibers up to the neocortex, the seat of higher cognitive functions. Now, scientists have discovered a key mechanism of this migration – one that may also play an important role in other developmental processes and diseases, including cancer.

The finding, the cover story in a recent issue of *Nature* (Aug. 23, 2007), was led by Laura Elias, a neuroscience graduate student in the laboratory of senior author Arnold Kriegstein, MD, PhD, a professor of neurology and director of the UCSF Institute for Regeneration Medicine.

Elias is one of 16 UCSF CIRM Stem Cell Scholars – up and coming young scientists funded by the California Institute for Regenerative Medicine, established by California voters in 2004 to allocate $3 billion over 10 years to support stem cell research.

Scientists have known that migration of neurons depends in part on motors within the cells that drive their movement along the neural stem cell fibers. They have also known that this migration depends on receptors on the neurons' surface that sense signals in the environment that either repel or attract the cells, thus directing their path.

But little has been known about the molecules that mediate the interaction between the migrating neurons and the neural stem cell fiber itself. And relatively overlooked in this process has been the possible

role of so-called “gap junctions.”

Gap junctions are pores, or channels, that form between cells. They are created when two hemi-channels, each in the membrane of a different cell, connect. The junctions are well known for their role in enabling cells to pass molecular signals to one another. In developing tissue, they are particularly active in supporting signaling that promotes cell proliferation, or cell division.

In the current study, however, the team made the unexpected finding that gap junctions also play a crucial role in neuronal migration – and that they function in a previously unrecognized way. Rather than functioning as a conduit through which molecular signals move, the two fused hemi-channels serve as a form of adhesion between the migrating neurons and the neural stem cell fibers.

Cell adhesion is a common mechanism, but its function had not been detected previously in gap junctions.

The discovery that gap junctions were involved in migration in any capacity was a surprise. Elias had been investigating whether the molecule functioned as a channel to regulate cell proliferation within embryonic neural stem cells of the developing rat brain, building on preliminary findings from the Kriegstein lab 15 years ago.

As part of one study, she had reduced the levels of gap junctions in the neural stem cells. “To our surprise,” she says, “the newborn neurons that the stem cells produced piled up on one another and failed to migrate into the cortex.”

To establish the role that gap junctions might play in neuronal migration, the team focused on the activity of the molecule’s subunits, known as connexons, in a series of studies in the developing rat brain. They honed

in on two of these proteins – Cx26 and Cx43 – because they determined that they were expressed at high levels in migrating neurons and along radial fibers and that they were, in fact, highly localized in regions of the neurons that were in contact with radial fibers.

In a notable finding, says Elias, blocking the activity of either subunit significantly impaired migration to the neocortex, as seen in a "striking cellular redistribution pattern of the neurons."

To determine the mechanism by which the gap junctions were functioning, the team selectively blocked three plausible mechanisms: the well-known channel function, a form of cellular signaling that relies on the intracellular end of the molecule, and adhesion.

"Remarkably," says co-author Doris Wang, a student in the MD, PhD neuroscience program at UCSF and a member of the Kriegstein lab, "we found that adhesion, alone, is necessary for the role of gap junctions during neuronal migration."

Further study revealed that the Cx43 and Cx26 molecular subunits interact with the neuron's internal cytoskeleton to stabilize it on its path.

A series of time-lapse, live imaging studies of migrating neurons illuminated this phenomenon: The neurons start out with a branched leading process. Then one of the processes is stabilized and the neuron translocates its body into a swelling that forms in the stabilized leading process. When the levels of the gap junction protein are reduced, however, the neurons are no longer able to stabilize their leading processes and continue to send out multiple branches.

The revelation of the gap junction's role in neural migration is provocative, says Kriegstein, because the molecule is known to be involved in several disease processes, including the spread of cancers in

the brain, skin and lung. Most brain tumors are made up of glial cells that spread throughout the brain by migrating along white matter pathways -- the network of neural fibers that connect neurons.

While roles for the gap junction channel in cancer have been demonstrated, “It’s possible,” he says, “that gap junctions are also using the cell adhesion function in these disease settings to support cell migration. If so, the mechanism could become a target for therapy.”

The study also revealed another surprising phenomenon, says Kriegstein, the John G. Bowes Endowed Chair in Stem Cell and Tissue Biology. It has long been known that when neural stem cells divide they undergo a process of asymmetrical division, in which they produce one newborn neuron and one new neural stem cell. The understanding has been that the neurons then begin their migration along the radial fibers to the neocortex.

But the study revealed that newborn neurons and the newborn neural stem cell stick together for a significant period of time, up to many days, while the newborn neuron migrates to the cortex, and they are stuck together by the gap junctions. It’s possible, says Kriegstein, that the adhesion function is allowing the gap junction to also support signaling through the gap junction channel between the neural stem cell and its daughter neuron.

The discovery of the gap junction’s adhesion capacity also offers a window into its evolutionary history, says Kriegstein. “The molecule may have been functioning for some time as an adhesion molecule,” he says. “It couldn’t very well form a channel between two neighboring cells unless the two halves of the channel first stuck together.”

The team’s understanding of neuronal migration in the developing brain also appears likely to evolve. The discoveries they’ve made in this study,

like the processes of the migrating neuron, are moving them forward with new hypotheses to investigate.

Source: University of California - San Francisco

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