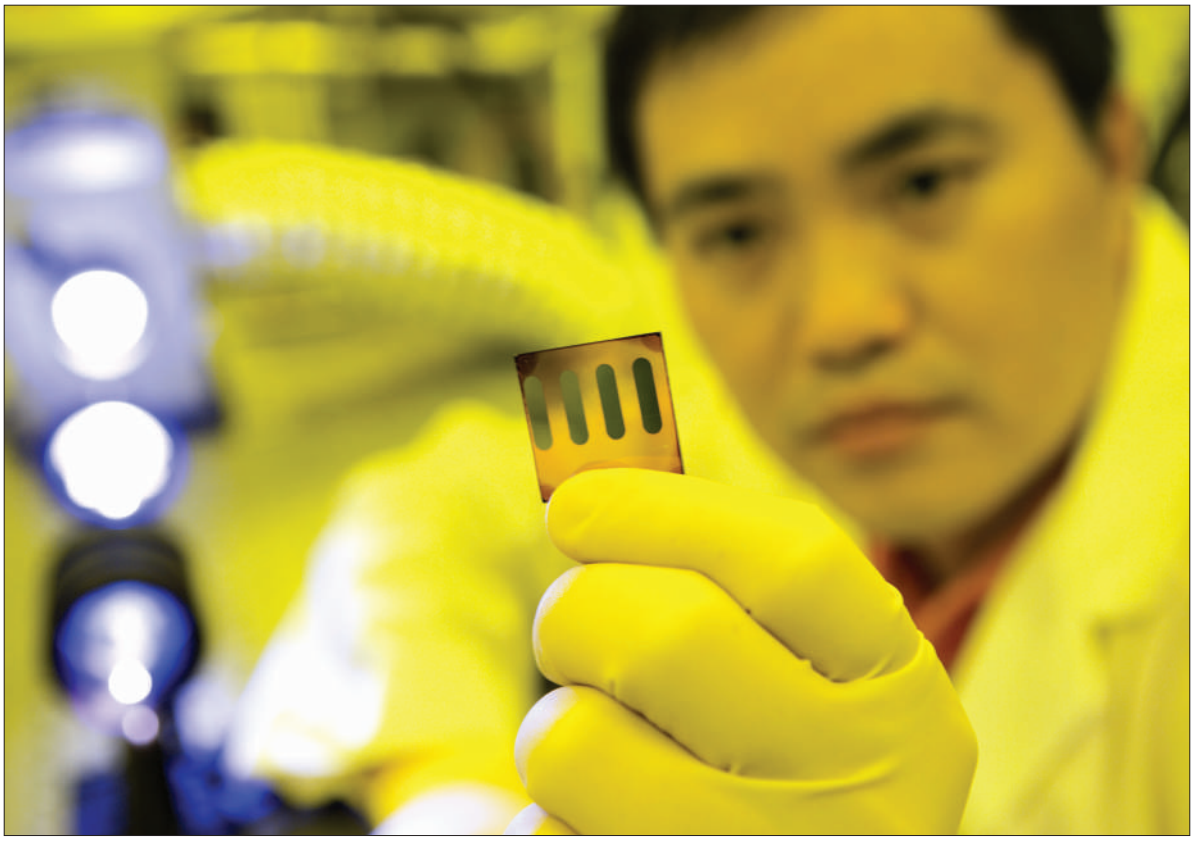

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Neural Stem Cells Maintain High Levels of Reactive Oxygen Species, Study Finds

For years, the majority of research on Reactive Oxygen Species (ROS) -- ions or very small molecules that include free radicals -- has focused on how they damage cell structure and their potential link to stroke, cardiovascular disease and other illnesses.

However, researchers at the Eli and Edy the Broad Center of Regenerative Medicine and Stem Cell Research have shown for the first time that neural stem cells, the cells that give rise to neurons, maintain high levels of ROS to help regulate normal self-renewal and differentiation.

The findings, published in the Jan. 7, 2011 issue of the journal Cell Stem Cell, may have significant implications for brain repair and abnormal brain development.

"Everyone thinks of ROS as things that kill cells, and they do," said Dr. Harley Kornblum, a Professor at the Intellectual and Developmental Disabilities Research Center in the Semel Institute of Neuroscience and Behavior and senior author of the study. "Stem cells generally have been thought to maintain low levels of ROS to protect against damage, so our findings were surprising and we hope to be able to exploit this to promote neural repair and explore diseases such as autism and brain cancer."

The study also found that the neural stem cells were highly responsive to ROS stimulation, which increased their growth and differentiation. Conversely, diminishing cellular levels of ROS in the neural stem cells interfered with normal cell function in mice and in human and mouse cell lines.

"It wasn't just that neural stem cells maintained high ROS levels" said Janel Le Belle, an Assistant Researcher in Kornblum's lab and lead author of the study. "Changes in cellular ROS can affect, how the stem cells function? This study could lead to an understanding of how elevated ROS due to environmental factors might play a role in brain overgrowth, such as occurs in some cases of autism."

The body has a system to make ROS when it needs it. Some cells, such as immune cells, surround bacteria or viruses and use ROS to kill the invading microbes. Outside influences such as stress and environmental factors such as exposure to radiation can increase ROS levels in cells.

Although ROS is produced by all cells in a passive manner as a by-product of normal cell metabolism, some cells also produce ROS in a directed manner using ROS-producing enzymes like NADPH oxidase (NOX). NOX-generated ROS can act as second messengers in tightly controlled signal transduction pathways for many growth and trophic factors. However, too much ROS damages and ultimately kills cells, so finding the correct balance is vital, Kornblum said. And in fact, when the neural stem cells in the study were given too much ROS, they did die.

Kornblum and his team also found that the ROS-mediated stem cell self-renewal and differentiation of these cells into neurons depended on a cell signaling pathway called PI3K/Akt, which is known to be involved in cellular functions such as cell growth, proliferation, differentiation, motility and survival. NOX-generated ROS affect PI3K/Akt signaling by causing the inactivation of the PTEN protein, an important tumor suppressor and negative regulator of the pathway, by oxidizing a cysteine residue in the protein, which inactivates its function.

Kornblum and his collaborators at UCLA, including Dr. Hong Wu, a Professor of Molecular and Medical Pharmacology and a co-author of the study, have been studying the PI3K pathway for years. The pathway is activated in some diseases, for example a subset of autism cases and in tuberous sclerosis, a rare, multi-system genetic disease

that causes non-malignant tumors to grow in the brain and in other vital organs. The pathway also can be activated in certain cancers.

"One of our hypotheses is that in these disease states, for instance in autism, that in those with a genetic predisposition to PI3K activation, exposure to a stressor that increases ROS levels can exacerbate the predisposition, perhaps promoting the disease," Kornblum said.

In brain tumors, if the pathway gets activated in cells already susceptible to becoming cancerous, it may promote the proliferation of brain tumor cells or the propagation of brain tumors. Blocking the pathway, Kornblum said, may be one way to interrupt the malignant process.

Going forward, Kornblum and his team will seek to determine whether brain cancer cells use elevated ROS and the PI3K pathway to promote their own growth. Le Belle said they will also test whether elevated ROS during brain development can contribute to brain overgrowth in Autism. Additionally, the team will test to see if they can exploit the ROS-activated pathway to promote brain repair, for example, increasing the production of new neurons to replace damaged or dead neurons.

The five-year study was funded by the National Institutes of Mental Health, Cure Autism Now, Autism Speaks, the UCLA CART, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation and the Koh Charitable Foundation.

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