

Role of gene in maintaining brain cell 'repair supplies' identified

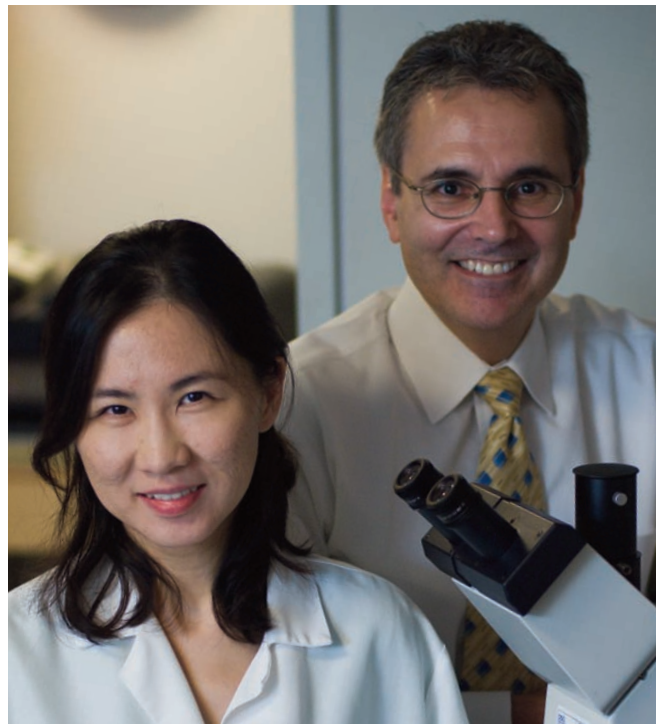
Like an electrician's supply closet of wires, fuse-boxes, switches, and sockets, the brain holds a reservoir of stem cells that generate new nerve cells during the course of aging and in the aftermath of brain injury. For these neural stem cells (NSCs) to have a long lifespan, they must spend a good deal of their time in a resting, or "quiescent," state, when they aren't dividing.

In a study published in the November issue of *Cell Stem Cell*, Dana-Farber scientists Ji-Hye Paik, PhD, Ronald DePinho, MD, and their colleagues report that a family of genes known as *FoxOs* play a key role in maintaining the body's reserves of NSCs. In concert with other genes, the *FoxOs* control the pace at which NSCs proliferate and renew themselves, ensuring the cells have the "down time" they need for a lengthy life.

The discovery suggests new avenues for treating a variety of developmental disorders, including microcephaly, a genetic condition involving abnormal smallness of the brain and head. One of the genes switched on by *FoxOs* influences brain size in mice and humans, suggesting that *FoxOs* may one day be used in correcting gene-driven brain abnormalities.

"Identifying and understanding the genes and pathways that govern stem cell reserves and their restorative functions may lead to better treatments for age-related degenerative diseases of the brain, and for tissue damage resulting from chemo or radiation therapy for cancer," Paik says.

The study is notable for the thoroughness with which researchers' proved the role of *FoxOs* in maintaining NSCs. They showed that mice bred with *FoxO* mutations had unusually large brains and high levels of NSCs shortly after birth, but experienced a premature and sharp drop in



Research by Ji-Hye Paik (left) and Ronald DePinho may lead to better treatments for age-related degenerative disease of the brain.

their ability to generate new brain cells as they matured. In other experiments, they put NSCs with *FoxO* mutations through a gauntlet of three different types of analysis, identifying the genes switched on by *FoxOs* and the nature of their job within the cell.

"The results of all these experiments converged to demonstrate that *FoxOs* interact with a diverse set of genes to ensure that NSCs divide at the appropriate rate," says Paik. "The study substantially increases our understanding of these genes that play a vital role in our health as we age." RL