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Switching off Aging in Stem Cells

A single molecular switch plays a central role in inducing stem cells in the brain, pancreas, and blood to lose function as they age, researchers have found. Mice lacking that switch show considerably reduced aging-related decline in stem cell function and tissue regeneration.

People tend to think that old tissues have less regenerative capacity because they are wearing out, said Sean J. Morrison, a Howard Hughes Medical Institute investigator at the University of Michigan who led the study of the switch's role in the brain. This work shows that they are not just wearing out; they are actively shutting themselves down.

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While the finding could ultimately lead to drugs to slow or reverse degeneration in the brain and other tissues, the researchers cautioned such treatments would have to be balanced against the chance of increasing cancer risk in patients. Stem cells are the immature progenitor cells that are the continuing self-renewing source of mature, differentiated cells in the body.

Morrison's study was published online September 6, 2006, in *Nature*, ahead of publication in the journal's print version, along with two other studies from independent research teams that studied how a protein called inhibitor of cyclin-dependent kinase 4A, or p16^{INK4a}, contributes to stem cell decline. The other papers reported studies of the gene's role in stem cell decline in insulin-producing pancreatic islet cells and hematopoietic stem cells, which generate blood cells. Those studies were headed, respectively, by Norman Sharpless of the University of North Carolina at Chapel Hill and David Scadden of Harvard University.

Before this work, p16^{INK4a} was thought of only as a gene that inhibited cancer formation by inducing senescence in the cell, said Morrison. The idea was that it wasn't expressed in normal tissues, and therefore probably didn't

have a physiological role but only came on when something went wrong in the cell.

However, said Morrison, studies in Sharpless's laboratory found that the gene becomes increasingly active as tissues age. That started us thinking that maybe this gene is part of why old tissues have less stem cell activity and less regenerative capacity, for example taking longer to heal, said Morrison. In our lab, for example, we've found that the brain makes fewer neurons with age, but the molecular mechanism for that effect was not known.

Morrison and his colleagues followed stem cell activity in the brains of normal mice as they aged. The researchers analyzed a particular area of the forebrain, the subventricular zone, known to be an important center of neuronal production, called neurogenesis, in adults. The other two research teams studied pancreatic islet cells and hematopoietic stem cells for the same reason - that they are a constant source of new cells in the adult.

Morrison and his colleagues found that stem cell number and self-renewal function, as well as neurogenesis, declined with age in the mice. But they found that during aging, p16^{INK4a} gene activity increased.

However, in genetically engineered mice that were deficient in p16^{INK4a}, stem cell function and neuronal production were enhanced in old but not young mice as compared to normal mice. We didn't turn an old brain into a young brain by deleting p16^{INK4a}, but the deficient mice did show significantly increased progenitor cell function and neurogenesis with age, compared to normal mice, said Morrison. This tells us that p16^{INK4a} is not the whole story, although it's an important part, and that other genes also regulate the aging process.

Morrison and his colleagues also found evidence that the gene does not play the same role in other neural tissues. There are different kinds of stem cells in different regions of the brain, and some of those stem cells are more sensitive to factors like p16^{INK4a} than others, said Morrison. p16^{INK4a} deficiency did not prevent the atrophy of the cortex that normally occurs with aging, they found. Nor did the deficiency prevent loss of function in another brain region, the hippocampus, that is also a center for neurogenesis in adults. The researchers also analyzed peripheral nerve cells in the gut and found that p16^{INK4a} did not prevent loss of stem cell function there. There are probably other factors that are important for aging of the hippocampus and the peripheral nervous system, Morrison noted.

Nevertheless, he said, the discovery of the central role of p16^{INK4a} is highly significant. I think if you asked before these studies whether you could delete a single gene and rescue stem cell function in multiple tissues, and neurogenesis in an old brain, many people would have said that aging is such a complex phenomenon that you would not get a significant effect, he said.

Morrison theorized that p16^{INK4a} is a suppressor of stem cell function that evolved as part of the regulatory machinery that also includes proto-oncogenes that encourage cell proliferation. We are all evolutionarily

selected to, on the one hand, maintain regenerative capacity of our tissues through adult life so that we can repair our cells and survive injuries — while on the other hand, limit proliferation in our tissues with age, so cells don't divide out of control, causing cancers, he said. And the way that we achieve that balance is by having proto-oncogenes that promote proliferation come into balance with tumor suppressor genes that inhibit proliferation. This work shows one way that this balance changes with age.

While these tumor suppressor mechanisms don't even exist during fetal development, where cells must divide rapidly, it makes sense that they become stronger in old age, when we are more at risk of getting a cancer, said Morrison. So, the benefit is that genes like p16 allow us to get older before we get cancer, but the bad news is that they make us lose function with age.