Studies Find General Mechanism of Cellular Aging

September 6 2006

Three separate studies confirm a gene that suppresses tumor cell growth also plays a key role in aging.

The researchers found increasing concentration, or expression, of the gene p16INK4a in older cells; these aging cells worked poorly compared to young cells and remembered their “age” even when transferred from old mice to young mice. The cells of mice bred without the gene showed less sluggishness as the animals aged and continued to function in a manner more similar to cells from younger mice.

Teams from the medical schools at the University of North Carolina at Chapel Hill, University of Michigan and Harvard University observed similar results in pancreatic islet cells and brain and blood stem cells.

The results show disparate cell types share a common aging mechanism and suggest that aging-related diseases such as diabetes result from a failure of cell growth, said Dr. Norman E. Sharpless, co-author on the three studies and an assistant professor of medicine and genetics at the UNC School of Medicine. “The studies indicate that certain stem cells lose their ability to divide and replace themselves with age as the expression of p16INK4a increases,” said Sharpless, a member of the UNC Lineberger Comprehensive Cancer Center.

The trio of reports are published online Sept. 6 in the journal *Nature*. The three research teams are from the medical schools at UNC, the University of Michigan and Harvard University.

The UNC study focused on p16INK4a effects on the function of pancreatic islet cells. Islet cells are responsible for insulin production and secretion. Because p16INK4a stops cancer cells from dividing and demonstrates increased expression with age, the scientists suspected the gene played a similar role in aging. The researchers developed strains of mice that were either deficient in p16INK4a (the gene was deleted, or 'knocked out") or genetically altered to have an excess of the protein to a degree seen in aging.

According to Sharpless, islet proliferation persisted in p16INK4a -deficient animals as they aged, "almost as if they were younger animals." In mice with an excess of p16INK4a, "islet cells aged prematurely; they stopped dividing early."

"This suggests that if we could attenuate p16INK4a expression in some way in humans, it could lead to enhanced islet re-growth in adults and a possible new treatment for diabetes," Sharpless said.

Similar results were found in the other studies, which focused on brain stem cells and blood stem cells.

The Michigan researchers, led by Dr. Sean Morrison, examined the role played by p16INK4a in neural stem cells, progenitor cells that can form new neurons and other brain cells. The team showed that p16INK4a increases markedly in those cells with aging. Moreover, p16INK4a -deficient neural stem cells work better and don't age to the same extent that wild-type (normal) stem cells do, Sharpless said.
Dr. Janakiraman Krishnamurthy, lead author of the UNC study and a postdoctoral scientist in the Sharpless lab, was a co-author of the Michigan report.

The Harvard team, led by Dr. David Scadden, studied the role of p16INK4a in hematopoietic stem cells, which proliferate continuously

during the adult lifespan and produce massive amounts of new blood cells on an hourly basis. Their results suggest that p16INK4a is the molecular basis for an old-age "signal" previously observed in blood stem cells. The Harvard study also showed that blood stem cells from old mice lacking p16INK4a functioned better than old cells from wild-type mice, suggesting p16INK4a causes aging of these cells as well.

Sharpless cautions that any promise of a potential new aging treatment based on p16INK4a should include two important caveats. "First, even though old mice lacking p16INK4a show enhanced stem cell function, they do not live longer. This is because p16INK4a is an important cancer-suppressor gene, and mice lacking p16INK4a develop more cancers than old, normal mice," he said.

"Secondly, in all three studies, p16INK4a loss was associated with an improvement in some but not all of the consequences of aging. There are clearly things in addition to p16INK4a that contribute to aging. We don't yet know what they are."

However, the gene may prove immediately useful as a biomarker for studies of aging, Sharpless said. "If you were going to calorically restrict yourself or take green tea or resveratrol every day for years in an effort to prevent aging, wouldn't you like some evidence that these not entirely benign things were having a beneficial effect? Now we have a biomarker that can directly test the effects of such things," he said.

UNC filed a patent on the use of p16INK4a as a biomarker of human aging in 2004. Co-inventors of the patent are Sharpless and Krishnamurthy.

Other authors of the UNC study are UNC graduate student Matthew R. Ramsey; Dr. Keith L. Ligon, pathologist at Brigham and Women's Hospital and Harvard Medical School in Boston; Chad Torrice,

technician in the Sharpless lab; Dr. Angela Koh, postdoctoral scientist at the Joslin Diabetes Center and Harvard Medical School; and Dr. Susan Bonner-Weir, also of the Joslin Diabetes Center and Harvard Medical School.

Source: University of North Carolina at Chapel Hill School of Medicine