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Scientists turn back the clock on adult stem cells aging

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Researchers have shown they can reverse the aging process for human adult stem cells, which are responsible for helping old or damaged tissues regenerate. The findings could lead to medical treatments that may repair a host of ailments that occur because of tissue damage as people age. A research group led by the Buck Institute for Research on Aging and the Georgia Institute of Technology conducted the study in cell culture, which appears in the September 1, 2011 edition of the journal *Cell Cycle*.

The regenerative power of tissues and organs declines as we age. The modern day stem cell hypothesis of aging suggests that living organisms are as old as are its tissue specific or adult stem cells. Therefore, an understanding of the molecules and processes that enable human adult stem cells to initiate self-renewal and to divide, proliferate and then differentiate in order to rejuvenate damaged tissue might be the key to regenerative medicine and an eventual cure for many age-related diseases. A research group led by the Buck Institute for Research on Aging in collaboration with the Georgia Institute of Technology, conducted the study that pinpoints what is going wrong with the biological clock underlying the limited division of human adult stem cells as they age.

"We demonstrated that we were able to reverse the process of aging for human adult stem cells by intervening with the activity of non-protein coding RNAs originated from genomic regions once dismissed as non-functional 'genomic junk'," said Victoria Lunyak, associate professor at

the Buck Institute for Research on Aging.

Adult stem cells are important because they help keep human tissues healthy by replacing cells that have gotten old or damaged. They're also multipotent, which means that an adult stem cell can grow and replace any number of body cells in the tissue or organ they belong to. However, just as the cells in the liver, or any other organ, can get damaged over time, adult stem cells undergo age-related damage. And when this happens, the body can't replace damaged tissue as well as it once could, leading to a host of diseases and conditions. But if scientists can find a way to keep these adult stem cells young, they could possibly use these cells to repair damaged heart tissue after a heart attack; heal wounds; correct metabolic syndromes; produce insulin for patients with type 1 diabetes; cure arthritis and osteoporosis and regenerate bone.

The team began by hypothesizing that DNA damage in the genome of adult stem cells would look very different from age-related damage occurring in regular body cells. They thought so because body cells are known to experience a shortening of the caps found at the ends of chromosomes, known as telomeres. But adult stem cells are known to maintain their telomeres. Much of the damage in aging is widely thought to be a result of losing telomeres. So there must be different mechanisms at play that are key to explaining how aging occurs in these adult stem cells, they thought.

Researchers used adult stem cells from humans and combined experimental techniques with computational approaches to study the changes in the genome associated with aging. They compared freshly isolated human adult stem cells from young individuals, which can self-renew, to cells from the same individuals that were subjected to prolonged passaging in culture. This accelerated model of adult stem cell aging exhausts the regenerative capacity of the adult stem cells. Researchers looked at the changes in genomic sites that accumulate

DNA damage in both groups.

"We found the majority of DNA damage and associated chromatin changes that occurred with adult stem cell aging were due to parts of the genome known as retrotransposons," said King Jordan, associate professor in the School of Biology at Georgia Tech.

"Retroransposons were previously thought to be non-functional and were even labeled as 'junk DNA', but accumulating evidence indicates these elements play an important role in genome regulation," he added.

While the young adult stem cells were able to suppress transcriptional activity of these genomic elements and deal with the damage to the DNA, older adult stem cells were not able to scavenge this transcription. New discovery suggests that this event is deleterious for the regenerative ability of stem cells and triggers a process known as cellular senescence.

"By suppressing the accumulation of toxic transcripts from retrotransposons, we were able to reverse the process of human adult stem cell aging in culture," said Lunyak.

"Furthermore, by rewinding the cellular clock in this way, we were not only able to rejuvenate 'aged' human stem cells, but to our surprise we were able to reset them to an earlier developmental stage, by up-regulating the "pluripotency factors" – the proteins that are critically involved in the self-renewal of undifferentiated embryonic stem cells." she said.

Next the team plans to use further analysis to validate the extent to which the rejuvenated stem cells may be suitable for clinical tissue regenerative applications.

More information: Inhibition of activated pericentromeric SINE/Alu

repeat transcription in senescent human adult stem cells reinstates self-renewal. *Cell Cycle*, Volume 10, Issue 17, September 1, 2011

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