

Press Release from the National Institutes of Health (NIH)

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NIH researchers find new clues about aging

Genetic splicing mechanism triggers both premature aging syndrome and normal cellular aging

National Institutes of Health researchers have identified a new pathway that sets the clock for programmed aging in normal cells. The study provides insights about the interaction between a toxic protein called progerin and telomeres, which cap the ends of chromosomes like aglets, the plastic tips that bind the ends of shoelaces.

The study by researchers from the National Human Genome Research Institute (NHGRI) appears in the June 13, 2011 early online edition of the *Journal of Clinical Investigation*.

Telomeres wear away during cell division. When they degrade sufficiently, the cell stops dividing and dies. The researchers have found that short or dysfunctional telomeres activate production of progerin, which is associated with age-related cell damage. As the telomeres shorten, the cell produces more progerin.

Progerin is a mutated version of a normal cellular protein called lamin A, which is encoded by the normal LMNA gene. Lamin A helps to maintain the normal structure of a cell's nucleus, the cellular repository of genetic information.

In 2003, NHGRI researchers discovered that a mutation in LMNA causes the rare premature aging condition, progeria, formally known as known as Hutchinson-Gilford progeria syndrome. Progeria is an extremely rare disease in which children experience symptoms normally associated with advanced age, including hair loss, diminished subcutaneous fat, premature atherosclerosis and skeletal abnormalities. These children typically die from cardiovascular complications in their teens.

"Connecting this rare disease phenomenon and normal aging is bearing fruit in an important way," said NIH Director Francis S. Collins, M.D., Ph.D., a senior author of the current paper. "This study highlights that valuable biological insights are gained by studying rare genetic disorders such as progeria. Our sense from the start was that progeria had a lot to teach us about the normal aging process and clues about more general biochemical and molecular mechanisms."

Collins led the earlier discovery of the gene mutation responsible for progeria and subsequent advances at NIH in understanding the biochemical and molecular underpinnings of the disease.

In a 2007 study, NIH researchers showed that normal cells of healthy people can produce a small amount of progerin, the toxic protein, even when they do not carry the mutation. The more cell divisions the cell underwent, the shorter the telomeres and the greater the production of progerin. But a mystery remained: What was triggering the production of the toxic progerin protein?

The current study shows that the mutation that causes progeria strongly activates the splicing of lamin A to produce the toxic progerin protein, leading to all of the features of premature aging suffered by children with this disease. But modifications in the splicing of LMNA are also at play in the presence of the normal gene.

The research suggests that the shortening of telomeres during normal cell division in individuals with normal LMNA genes somehow alters the way a normal cell processes genetic information when turning it into a protein, a process called RNA splicing. To build proteins, RNA is transcribed from genetic instructions embedded in DNA. RNA does not carry all of the linear information embedded in the ribbon of DNA; rather, the cell splices together segments of genetic information called exons that contain the code for building proteins, and removes the intervening letters of unused genetic information called introns. This mechanism appears to be altered by telomere shortening, and affects protein production for multiple proteins that are important for cytoskeleton integrity. Most importantly, this alteration in RNA splicing affects the processing of the LMNA messenger RNA, leading to an accumulation of the toxic progerin protein.

Cells age as part of the normal cell cycle process called senescence, which progressively advances through a limited number of divisions in the cell lifetime. "Telomere shortening during cellular senescence plays a causative role in activating progerin production and leads to extensive change in alternative splicing in multiple other genes," said lead author Kan Cao, Ph.D., an assistant professor of cell biology and molecular genetics at the University of Maryland, College Park.

Telomerase is an enzyme that can extend the structure of telomeres so that cells continue to maintain the ability to divide. The study supplied support for the telomere-progerin link, showing that cells that have a perpetual supply of telomerase, known as immortalized cells, produce very little progerin RNA. Most cells of this kind are cancer cells, which do not reach a normal cell cycle end point, and instead replicate out of control.

The researchers also conducted laboratory tests on normal cells from healthy individuals using biochemical markers to indicate the occurrence of progerin-generating RNA splicing in cells. The cell donors ranged in age from 10 to 92 years. Regardless of age, cells that passed through many cell cycles had progressively higher progerin production. Normal cells that produce higher concentrations of progerin also displayed shortened and dysfunctional telomeres, the tell-tale indication of many cell divisions.

In addition to their focus on progerin, the researchers conducted the first systematic analysis across the genome of alternative splicing during cellular aging, considering which other protein products are affected by jumbled instructions as RNA molecules assemble proteins through splicing. Using laboratory techniques that analyze the order of chemical units of RNA, called nucleotides, the researchers found that splicing is altered by short telomeres, affecting lamin A and a number of other genes, including those that encode proteins that play a role in the structure of the cell.

The researchers suggest that the combination of telomere fraying and loss with progerin production together induces cell aging. This finding lends insights into how progerin may participate in the normal aging process.

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For more about Hutchinson-Gilford progeria syndrome, go to <http://www.genome.gov/11007255> <<http://www.genome.gov/11007255>> .