Buildup of damaged DNA in cells drives aging

December 20 2006

The accumulation of genetic damage in our cells is a major contributor to how we age, according to a study being published today in the journal *Nature* by an international group of researchers. The study found that mice completely lacking a critical gene for repairing damaged DNA grow old rapidly and have physical, genetic and hormonal profiles very similar to mice that grow old naturally.

Furthermore, the premature aging symptoms of the mice led to the discovery of a new type of human progeria, a rare inherited disease in which affected individuals age rapidly and die prematurely.

"These progeroid mice, even though they do not live very long, have remarkably similar characteristics to normal old mice, from their physical symptoms, to their metabolic and hormonal changes and pathology, right down to the level of similar changes in gene expression," said corresponding author Jan Hoeijmakers, Ph.D., head of the department of genetics at the Erasmus Medical Center in Rotterdam, Netherlands. "This provides strong evidence that failure to repair DNA damage promotes aging— a finding that was not entirely unexpected since DNA damage was already known to cause cancer. However, it shows how important it is to repair damage that is constantly inflicted upon our genes, even through the simple act of breathing."

The study found that a key similarity between the progeria-like, or progeroid, mice and naturally old mice is the suppression of genes that control metabolic pathways promoting growth, including those

controlled by growth hormone. How growth hormone pathways are suppressed is not known, but this response appears to have evolved to protect against stress caused by DNA damage or the wear-and-tear of normal living. The authors speculate that this stress response allows each of us to live as long and as healthy a life as possible despite the accumulation of genetic damage as we age.

Findings from this study help to reconcile two conflicting hypotheses currently favored in the field of aging research about why we get old, according to the authors. The first is that our lifespan and how well we age is determined by the genes inherited from our parents. The second is that lifespan and fitness in old age is determined by how much damage we incur over our lifetime.

"Our study suggests that both of these hypotheses are correct. Damage, including DNA damage, drives the functional decline we all experience as we age. But how we respond to that damage is determined genetically, in particular by genes that regulate the growth hormone and insulin pathways," said Laura Niedernhofer, M.D., Ph.D., assistant professor of molecular genetics and biochemistry, University of Pittsburgh School of Medicine, and first author of the study.

How the researchers came to study the relationship between DNA damage and aging began almost serendipitously in the late 1990s while Dr. Niedernhofer was a post-doctoral fellow in Dr. Hoeijmakers' laboratory at Erasmus Medical Center, a well-known European center for medical genetics, including the diagnosis of people with unusual sensitivity to sunlight.

A German physician had contacted the center about a 15-year old Afghan boy who was highly sensitive to the sun and had other debilitating symptoms including weight loss, muscle wasting, hearing loss, visual impairment, anemia, hypertension and kidney failure. The

boy's family had immigrated to Germany to seek better medical treatment for his condition.

Extreme sensitivity to ultraviolet (UV) radiation from sunlight is a hallmark of diseases caused by defective DNA repair—an important mechanism by which skin and other cell types normally cut out, or excise, damage to their DNA caused by UV light. Defects in one DNA repair mechanism, nucleotide excision repair (NER), causes xeroderma pigmentosum, a rare disease in which people have a 2,000-fold increased risk of skin cancer from sun exposure.

When the investigators obtained cells from the boy and tested them for NER activity, they found almost none. Further analysis of the boy's DNA revealed a mutation in a gene known as XPF, which codes for part of a key enzyme required for the removal of DNA damage. The XPF portion of the enzyme harbors the DNA-cutting activity; whereas a second portion, known as ERCC1, is essential for the enzyme to bind to the damaged DNA. Mutations in either XPF or ERCC1 lead to reduced activity of this key DNA repair enzyme.

"We were completely surprised by the finding that the patient had a mutation in XPF, because mutations in this gene typically cause xeroderma pigmentosum, which is a disease characterized primarily by skin and other cancers rather than accelerated aging," said Dr. Hoeijmakers. "This patient, therefore, has a unique disease, which we named XPF-ERCC1, or XFE-progeroid syndrome."

To understand why this XPF mutation caused accelerated aging, the investigators compared the expression pattern of all of the genes (approximately 30,000) in the liver of 15-day-old mice that had been generated in the laboratory to harbor a defect in their XPF-ERCC1 enzyme and that had symptoms of rapidly accelerated aging to the genes expressed by normal mice of the same age. This comparison revealed a

profound suppression of genes in several important metabolic pathways in the progeroid mice. Most notably, the progeroid mice had a profoundly suppressed somatotroph (growth hormone) axis—a key pathway involved in the promotion of growth and development—compared to normal mice.

The investigators also found low levels of growth hormones in the progeroid mice and ruled out the possibility that this suppression was due to problems with their hypothalamus or pituitary glands, which regulate growth hormone secretion. Furthermore, they demonstrated that if normal adult mice were exposed to a drug that causes DNA damage, such as a cancer chemotherapy agent, the growth hormone axis was similarly suppressed. In other words, DNA damage somehow triggered hormonal changes that halted growth, while also boosting maintenance and repair.

Because growth hormone levels go down as we get older, contributing to loss of muscle mass and bone density, the investigators systematically compared the gene expression pattern of their progeroid mice to normal old mice to look for other similarities. What they found was a striking similarity pattern between the progeroid and normal-aged mice in several key pathways.

Indeed, for genes that influence the growth hormone pathway, there was a greater than 95 percent correlation in changes in gene expression between the DNA repair-deficient mice and old mice. And, remarkably, there was a near 90 percent correlation between all other pathways affected in the progeroid mice and the older mice.

"Because there were such high correlations between these pathways in progeroid and normal older mice, we are quite confident that DNA damage plays a significant role in promoting the aging process. The bottom line is that avoiding or reducing DNA damage caused by sources

such as sunlight and cigarette smoke, as well as by our own metabolism, also could delay aging," explained Dr. Niedernhofer.

Source: University of Pittsburgh