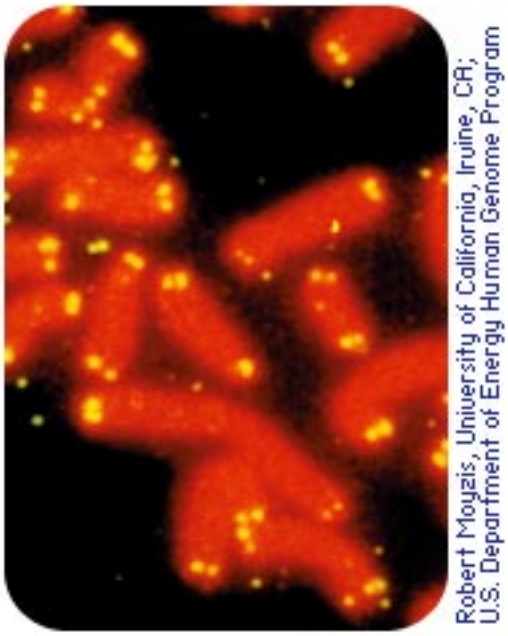
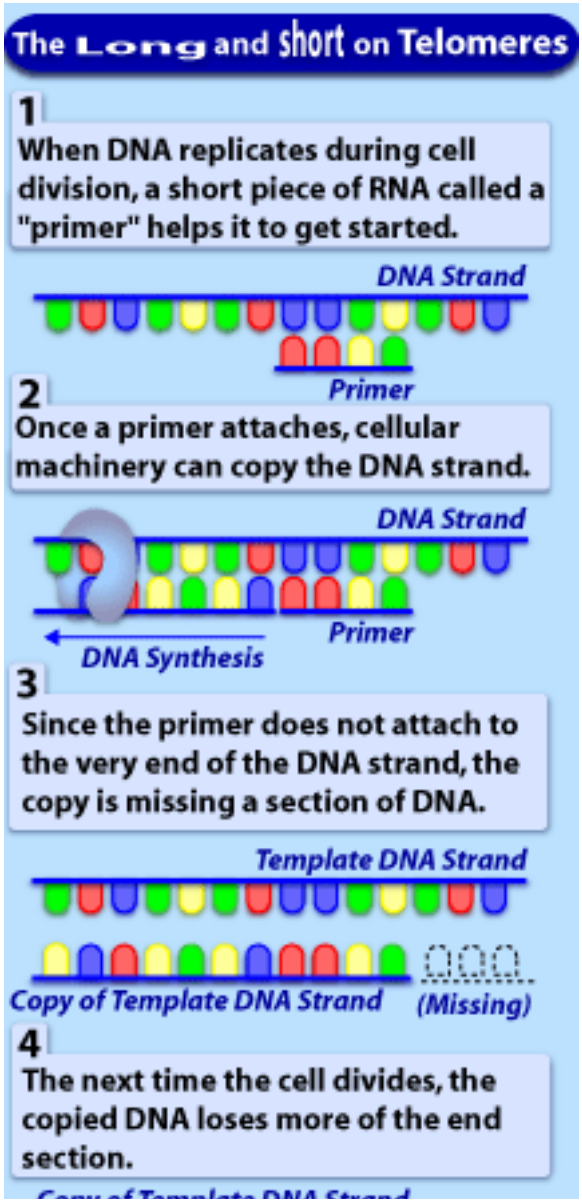
Genetic Science Learning Center at The University of Utah

Teacher Resources and **Lesson Plans**

Are Telomeres the Key to Aging and Cancer?



Fluorescence-stained chromosomes (red) on a microscope slide. Telomere sequences (yellow) reside at the ends of each chromosome.



Our genes carry the inherited blueprint that makes us what we are. Inside the center or nucleus of a cell, the genes are located on twisted, double-stranded molecules of DNA called chromosomes. At the ends of the chromosomes are stretches of DNA called telomeres, which protect our genetic data, make it possible for cells to divide and hold some secrets to

how we age and get cancer.

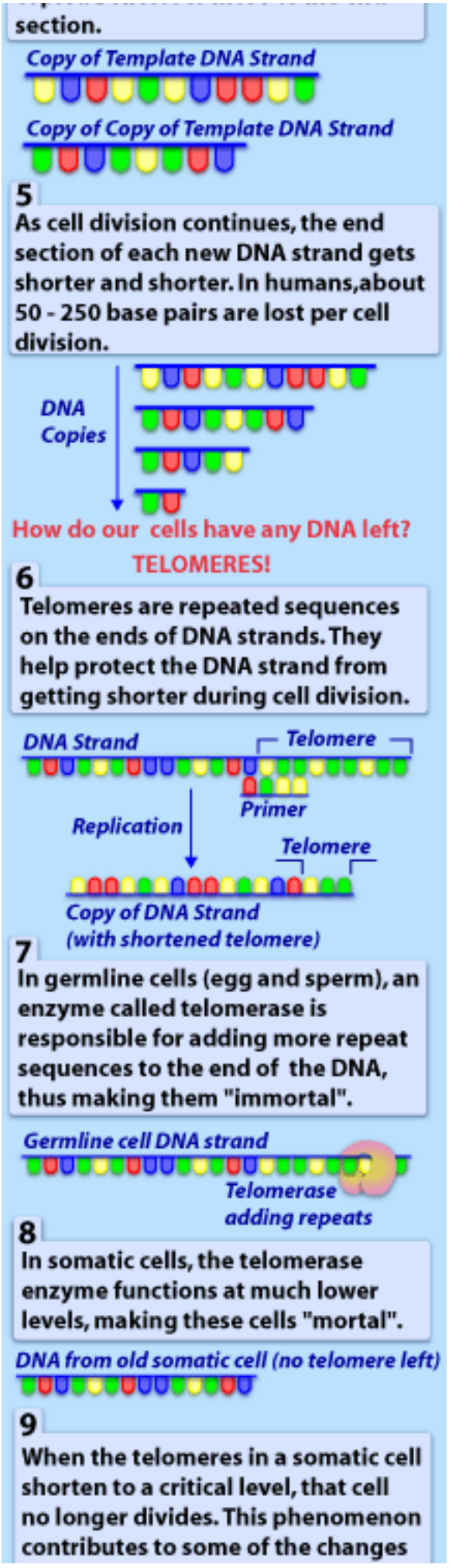
Telomeres have been compared with the plastic tips on shoelaces because they prevent chromosome ends from fraying and sticking to each other, which would scramble an organism's genetic information to cause cancer, other diseases or death.

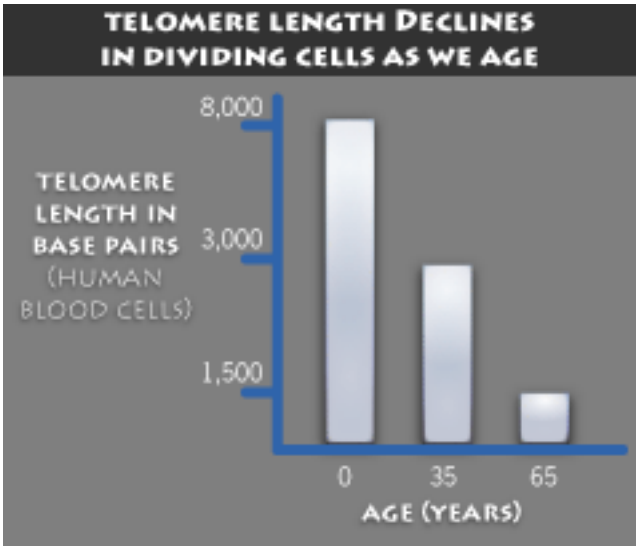
Yet, each time a cell divides, the telomeres get shorter. When they get too short, the cell no longer can divide and becomes inactive or "senescent" or dies. This process is associated with aging, cancer and a higher risk of death. So telomeres also have been compared with a bomb fuse.

What are telomeres?

Like the rest of a chromosome and its genes, telomeres are sequences of DNA - chains of chemical code. Like other DNA, they are made of four nucleic acid bases: G for guanine, A for adenine, T for thymine and C for cytosine.

Telomeres are made of repeating sequences of TTAGGG on one strand of DNA bound to AATCCC on the other strand. Thus, one section of telomere is a "repeat" made of six "base pairs."





In human blood cells, the length of telomeres ranges from 8,000 base pairs at birth to 3,000 base pairs as people age and as low as 1,500 in elderly people. (An entire chromosome has about 150 million base pairs.) Each time a cell divides, an average person loses 30 to 200 base pairs from the ends of that cell's telomeres.

Cells normally can divide only about 50 to 70 times, with telomeres getting progressively shorter until the cells become senescent, die or sustain genetic damage that can cause cancer.

Telomeres do not shorten with age in tissues such as heart muscle in which cells do not continually divide.

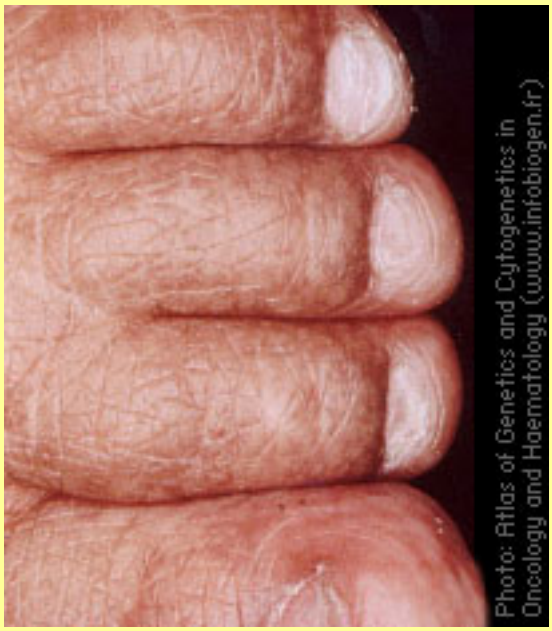
Why do chromosomes have telomeres?

Without telomeres, the main part of the chromosome - the part containing genes essential for life - would get shorter each time a cell divides. So telomeres allow cells to divide without losing genes. Cell division is needed so we can grow new skin, blood, bone and other cells when needed.

no longer divides. This phenomenon contributes to some of the changes we see in aging.

Do telomeres play a role in other diseases?

People with a disease named dyskeratosis congenita have telomeres that get short much more quickly than normal. These people endure premature aging and death. They face a higher risk of life-threatening infections, leukemia and other blood cancers, intestinal disorders, cirrhosis of the liver and pulmonary fibrosis, a deadly stiffening of lung tissue. They also are more likely to endure gray hair, balding, poor wound healing, spots on the skin, intestinal disorders, softening of the bones and learning disabilities. The implication is that telomeres may play a role in all those conditions because they all involve tissues in which cells divide often. There also is some evidence linking shortened telomeres to Alzheimer's disease, hardening of the arteries, high blood pressure and type II diabetes.



Signs of dyskeratosis can include mis-formed nails, altered skin pigmentation and hair loss.

Additional Resources

Without telomeres, chromosome ends could fuse together and degrade the cell's genetic blueprint, making the cell malfunction, become cancerous or die. Because broken DNA is dangerous, a cell has the ability to sense and repair chromosome damage. Without telomeres, the ends of chromosomes would look like broken DNA, and the cell would try to fix something that wasn't broken. That also would make them stop dividing and eventually die.

Why do telomeres get shorter each time a cell divides?

Before a cell can divide, the chromosomes within it are duplicated so that each of the two new cells contains identical genetic material. A chromosome's two strands of DNA must unwind and separate. An enzyme (DNA polymerase) then starts to make two new strands of DNA to match each of the two unwound strands. It does this with the help of short pieces of RNA. When each new matching strand is completed, it is a bit shorter than the original strand because of the room needed at the end by this small piece of RNA. It is like someone who paints himself into a corner and cannot paint the corner.

Does anything counteract telomere shortening?

An enzyme named telomerase adds bases to the ends of telomeres. In young cells, telomerase keeps telomeres from wearing down too much. But as cells divide repeatedly, there is not enough telomerase, so

American Federation for Aging Research

University of Utah news release on study of telomere shortening and mortality

Shay-Wright Laboratory at University of Texas Southwestern Medical Center

the telomeres grow shorter and the cells age.

Telomerase remains active in sperm and eggs, which are passed from one generation to the next. If reproductive cells did not have telomerase to maintain the length of their telomeres, any organism with such cells soon would go extinct.

What role do telomeres play in cancer?

As a cell begins to become cancerous, it divides more often, and its telomeres become very short. If its telomeres get too short, the cell may die. It can escape this fate by becoming a cancer cell and activating an enzyme called telomerase, which prevents the telomeres from getting even shorter.

Studies have found shortened telomeres in many cancers, including pancreatic, bone, prostate, bladder, lung, kidney, and head and neck.

Measuring telomerase may be a new way to detect cancer. If scientists can learn how to stop telomerase, they might be able to fight cancer by making cancer cells age and die. In one experiment, researchers blocked telomerase activity in human breast and prostate cancer cells growing in the laboratory, prompting the tumor cells to die. But there are risks. Blocking telomerase could impair fertility, wound healing, and production of blood cells and immune system cells.

What about telomeres and aging?

Dr. Richard Cawthon

Geneticist Richard Cawthon and colleagues at the University of Utah found shorter telomeres are associated with shorter lives. Among people older than 60, those with shorter telomeres were three times more likely to die from heart disease and eight times more likely to die from infectious disease.

While telomere shortening has been linked to the

aging process, it is not yet known whether shorter telomeres are just a sign of aging - like gray hair - or actually contribute to aging.

If telomerase makes cancer cells immortal, could it prevent normal cells from aging? Could we extend lifespan by preserving or restoring the length of telomeres with telomerase? If so, does that raise a risk the telomerase also will cause cancer?

Scientists are not yet sure. But they have been able to use telomerase to make human cells keep dividing far beyond their normal limit in laboratory experiments, and the cells do not become cancerous.

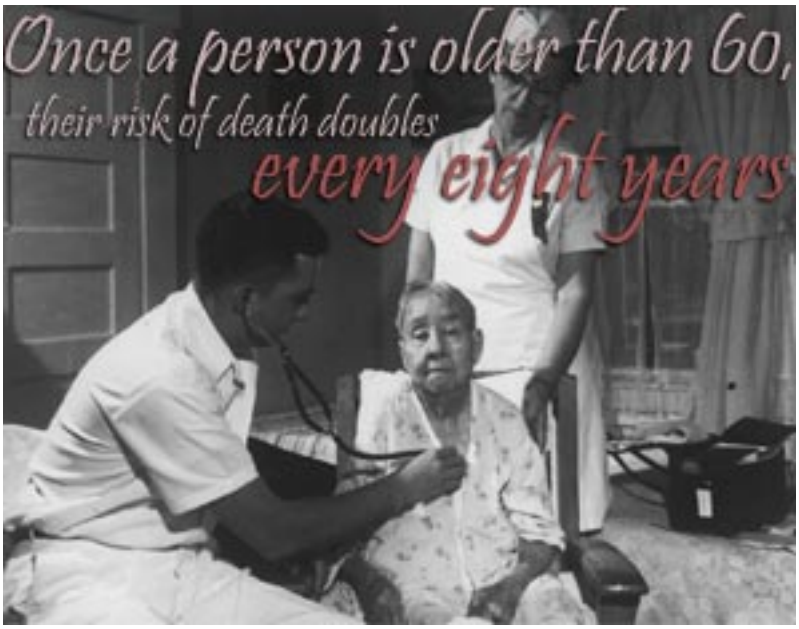
If telomerase could be used routinely to "immortalize" human cells, it would be theoretically possible to mass produce any human cell for transplantation, including insulin-producing cells to cure diabetes patients, muscle cells for muscular dystrophy, cartilage cells for people with certain kinds of arthritis, and skin cells for people with severe burns and wounds. Efforts to test new drugs and gene therapies also would be helped by an unlimited supply of normal human cells grown in the laboratory.

How big a role do telomeres play in aging?

Some long-lived species like humans have telomeres that are much shorter than species like mice, which live only a few years. Nobody yet knows why. But it's evidence that telomeres alone do not dictate lifespan.

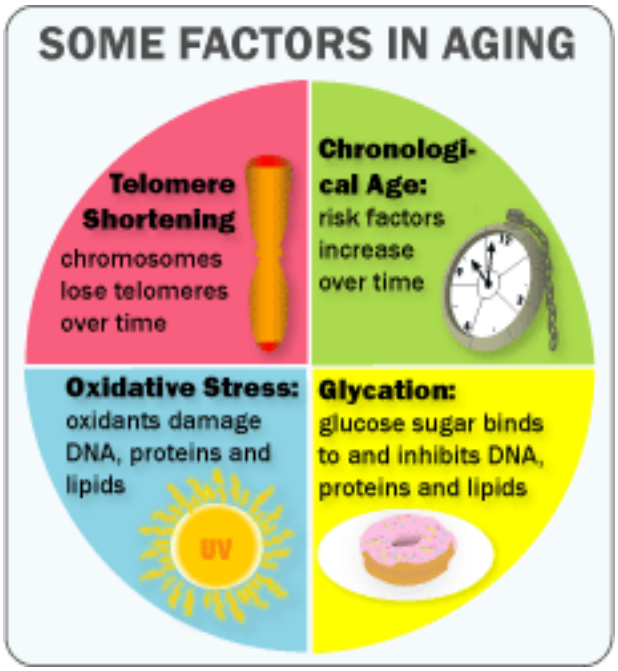
Cawthon's study found that when people are divided into two groups based on telomere lengths, the half with longer telomeres lives five years longer than those with shorter telomeres. That suggests lifespan could be increased five years by increasing the length of telomeres in people with shorter ones.

People with longer telomeres still experience telomere shortening as they age. How many years might be added to our lifespan by completely stopping telomere shortening? Cawthon believes 10 years and perhaps 30 years.



Once a person is older than 60, their risk of death doubles with every eight years of age. So a 68-year-old has twice the chance of dying within a year compared with a 60-year-old. Cawthon's study found that differences in telomere length accounted for only 4 percent of that difference. And while intuition tells us older people have a higher risk of death, only another 6 percent is due purely to chronological age. When telomere length, chronological age and gender are

combined (women live longer than men), those factors account for 37 percent of the variation in the risk of dying over age 60. So what causes the other 63 percent?



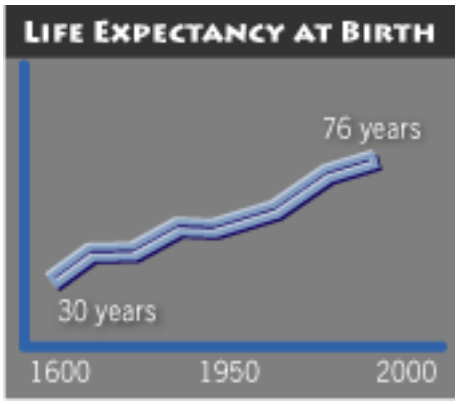
A major cause of aging is "oxidative stress." It is the damage to DNA, proteins and lipids (fatty substances) caused by oxidants, which are highly reactive substances containing oxygen. These oxidants are produced normally when we breathe, and also result from inflammation, infection and consumption of alcohol and cigarettes. In one study, scientists exposed worms to two substances that neutralize oxidants, and the worms' lifespan increased an average 44 percent.

Another factor in aging is "glycation." It happens when glucose sugar from what we eat binds to some of our DNA, proteins and lipids, leaving them unable to do their jobs. The problem becomes worse as we get older, causing body tissues to malfunction, resulting in disease and death. This may explain why studies in

various laboratory animals indicate that restricting calorie intake extends lifespan.

It is possible oxidative stress, glycation, telomere shortening and chronological age - along with various genes - all work together to cause aging?

What are the prospects for human immortality?



Human lifespan has increased considerably since the 1600s, when the average person lived no more than 30 years. By 1998, the average U.S. life expectancy was 76. The reasons included sewers and other sanitation measures, antibiotics, clean water, refrigeration, vaccines and other medical efforts to prevent children and babies from dying, improved diets and better health care.

Some scientists believe average life expectancy will continue to increase, although many doubt the average will exceed 90. But a few predict vastly longer lifespans are possible.

Cawthon says that if all processes of aging could be eliminated and oxidative stress damage could be repaired, "one estimate is people could live 1,000

years," and they would die from causes like accidents, suicide, murder and pneumonia and some other infectious diseases.

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