

Nobel Prize in Medicines 2009



Elizabeth H. Blackburn



Carol W. Greider



Jack W. Szostak

The Nobel Prize in Physiology or Medicine 2009 was awarded jointly to Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak "for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase".

This year's Nobel Prize in Physiology or Medicine is awarded to three scientists who have solved a major problem in biology: how the chromosomes can be copied in a complete way during cell divisions and how they are protected against degradation. The Nobel Laureates have shown that the solution is to be found in the ends of the chromosomes – the telomeres – and in an enzyme that forms them – telomerase.

The long, thread-like DNA molecules that carry our genes are packed into chromosomes, the telomeres being the caps on their ends. Elizabeth Blackburn and Jack Szostak discovered that a unique DNA sequence in the telomeres protects the chromosomes from degradation. Carol Greider and Elizabeth Blackburn identified telomerase, the enzyme that makes telomere DNA. These discoveries explained how the ends of the chromosomes are protected by the telomeres and that they are built by telomerase.

If the telomeres are shortened, cells age. Conversely, if telomerase activity is high, telomere length is maintained, and cellular senescence is delayed. This is the case in cancer cells, which can be considered to have eternal life. Certain inherited diseases, in contrast, are characterized by a defective telomerase, resulting in damaged cells. The award of the Nobel Prize recognizes the discovery of a fundamental mechanism in the cell, a discovery that has stimulated the development of new therapeutic strategies.

The mysterious telomere

The chromosomes contain our genome in their DNA molecules. As early as the 1930s, Hermann Muller (Nobel Prize 1946) and Barbara McClintock (Nobel Prize 1983) had observed that the structures at the ends of the chromosomes, the so-called telomeres, seemed to prevent the chromosomes from attaching to each other. They suspected that the telomeres could have a protective role, but how they operate remained an enigma.

When scientists began to understand how genes are copied, in the 1950s, another problem presented itself. When a cell is about to divide, the DNA molecules, which contain the four bases that form the genetic code, are copied, base by base, by DNA polymerase enzymes. However, for one of the two DNA strands, a problem exists in that the very end of the strand cannot be copied. Therefore, the chromosomes should be shortened every time a cell divides – but in fact that is not usually the case (Fig 1).

Both these problems were solved when this year's Nobel Laureates discovered how the telomere functions and found the enzyme that copies it.

Telomere DNA protects the chromosomes

In the early phase of her research career, Elizabeth Blackburn mapped DNA sequences. When studying the chromosomes of *Tetrahymena*, a unicellular ciliate organism, she identified a DNA sequence that was repeated several times at the ends of the chromosomes. The function of this sequence, CCCAA, was unclear. At the same time, Jack Szostak had made the observation that a linear DNA molecule, a type of minichromosome, is rapidly degraded when introduced into yeast cells.

Blackburn presented her results at a conference in 1980. They caught Jack Szostak's interest and he and Blackburn decided to perform an experiment that would cross the boundaries between very distant species (Fig 2). From the DNA of Tetrahymena, Blackburn isolated the CCCAA sequence. Szostak coupled it to the minichromosomes and put them back into yeast cells. The results, which were published in 1982, were striking – the telomere DNA sequence protected the minichromosomes from degradation. As telomere DNA from one organism, Tetrahymena, protected chromosomes in an entirely different one, yeast, this demonstrated the existence of a previously unrecognized fundamental mechanism. Later on, it became evident that telomere DNA with its characteristic sequence is present in most plants and animals, from amoeba to man.

An enzyme that builds telomeres

Carol Greider, then a graduate student, and her supervisor Blackburn started to investigate if the formation of telomere DNA could be due to an unknown enzyme. On Christmas Day, 1984, Greider discovered signs of enzymatic activity in a cell extract. Greider and Blackburn named the enzyme telomerase, purified it, and showed that it consists of RNA as well as protein (Fig 3). The RNA component turned out to contain the CCCAA sequence. It serves as the template when the telomere is built, while the protein component is required for the construction work, i.e. the enzymatic activity. Telomerase extends telomere DNA, providing a platform that enables DNA polymerases to copy the entire length of the chromosome without missing the very end portion.

Telomeres delay ageing of the cell

Scientists now began to investigate what roles the telomere might play in the cell. Szostak's group identified yeast cells with mutations that led to a gradual shortening of the telomeres. Such cells grew poorly and eventually stopped dividing. Blackburn and her co-workers made mutations in the RNA of the telomerase and observed similar effects in Tetrahymena. In both cases, this led to premature cellular ageing – senescence. In contrast, functional telomeres instead prevent chromosomal damage and delay cellular senescence. Later on, Greider's group showed that the senescence of human cells is also

delayed by telomerase. Research in this area has been intense and it is now known that the DNA sequence in the telomere attracts proteins that form a protective cap around the fragile ends of the DNA strands.

An important piece in the puzzle - human ageing, cancer, and stem cells

These discoveries had a major impact within the scientific community. Many scientists speculated that telomere shortening could be the reason for ageing, not only in the individual cells but also in the organism as a whole. But the ageing process has turned out to be complex and it is now thought to depend on several different factors, the telomere being one of them. Research in this area remains intense.

Most normal cells do not divide frequently, therefore their chromosomes are not at risk of shortening and they do not require high telomerase activity. In contrast, cancer cells have the ability to divide infinitely and yet preserve their telomeres. How do they escape cellular senescence? One explanation became apparent with the finding that cancer cells often have increased telomerase activity. It was therefore proposed that cancer might be treated by eradicating telomerase. Several studies are underway in this area, including clinical trials evaluating vaccines directed against cells with elevated telomerase activity.

Some inherited diseases are now known to be caused by telomerase defects, including certain forms of congenital aplastic anemia, in which insufficient cell divisions in the stem cells of the bone marrow lead to severe anemia. Certain inherited diseases of the skin and the lungs are also caused by telomerase defects.

In conclusion, the discoveries by Blackburn, Greider and Szostak have added a new dimension to our understanding of the cell, shed light on disease mechanisms, and stimulated the development of potential new therapies.

Elizabeth H. Blackburn has US and Australian citizenship. She was born in 1948 in Hobart, Tasmania, Australia. After undergraduate studies at the University of Melbourne, she received her PhD in 1975 from the University of Cambridge, England, and was a postdoctoral researcher at Yale University, New Haven, USA. She was on the faculty at the

University of California, Berkeley, and since 1990 has been professor of biology and physiology at the University of California, San Francisco.

Carol W. Greider is a US citizen and was born in 1961 in San Diego, California, USA. She studied at the University of California in Santa Barbara and in Berkeley, where she obtained her PhD in 1987 with Blackburn as her supervisor. After postdoctoral research at Cold Spring Harbor Laboratory, she was appointed professor in the department of molecular biology and genetics at Johns Hopkins University School of Medicine in Baltimore in 1997.

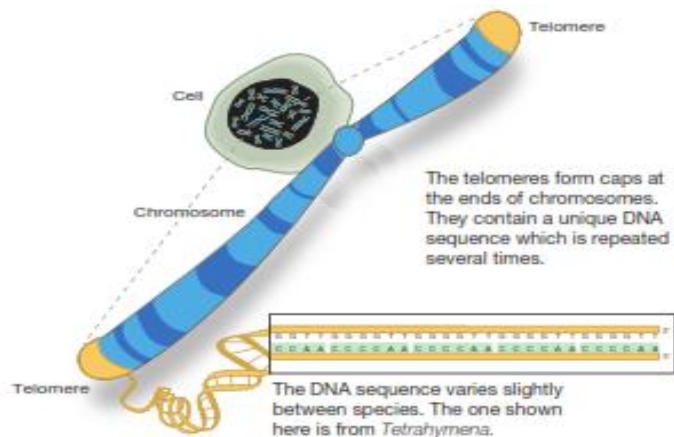
Jack W. Szostak is a US citizen. He was born in 1952 in London, UK and grew up in Canada. He studied at McGill University in Montreal and at Cornell University in Ithaca, New York, where he received his PhD in 1977. He has been at Harvard Medical School since 1979 and is currently professor of genetics at Massachusetts General Hospital in Boston. He is also affiliated with the Howard Hughes Medical Institute.

The Telomere – Function and Synthesis

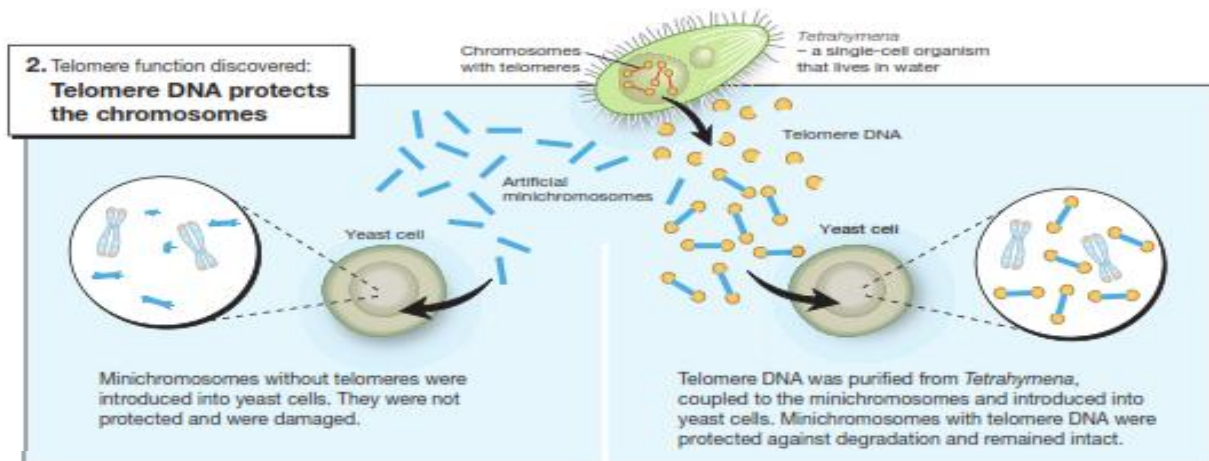
1. The mysterious telomere

The telomeres appear to protect the chromosomes from damage. But how?

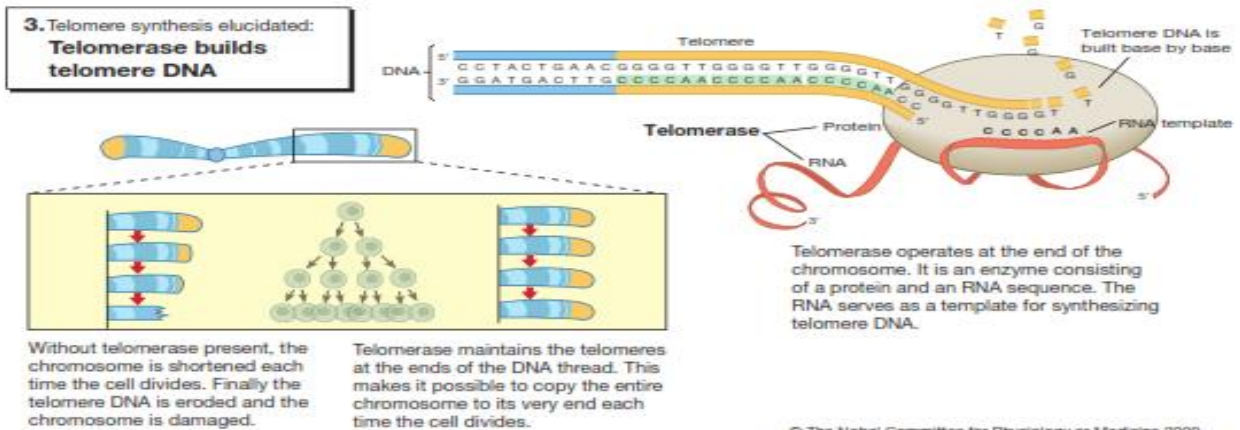
Telomere = Greek for "end" (telos) and "part" (meros)



2. Telomere function discovered: Telomere DNA protects the chromosomes



3. Telomere synthesis elucidated: Telomerase builds telomere DNA



For more details please visit:

http://www.nobelprize.org/nobel_prizes/medicine/laureates/2009/press.html

Call for research and Review articles publication: ijsidonlineinfo@gmail.com