

ADVERTISEMENT

Special offer for **RabMAB**[®]
购任意Abcam一抗, 享RabMAB[®] 兔单抗 超值优惠



SCIENTIFIC AMERICAN™

Permanent Address: <http://www.scientificamerican.com/article/telomeres-telomerase-and/>
Health » Features

This article is from the In-Depth Report [The 2009 Nobel Prizes](#)

Telomeres, Telomerase and Cancer [Reprint] [Preview]

An unusual enzyme called telomerase acts on parts of chromosomes known as telomeres. The enzyme has recently been found in many human tumors and is being eyed as a new target for cancer therapy

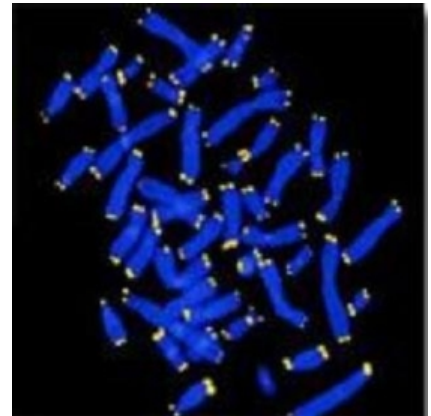
Oct 5, 2009 | By Carol W. Greider and Elizabeth H. Blackburn | 0

Editor's note: We are posting the main text of this article from the February 1996 issue of Scientific American for all our readers because the authors have won the 2009 Nobel Prize in Physiology or Medicine. Subscribers to the digital archive may obtain a full PDF version, complete with artwork and captions.

Often in nature things are not what they seem. A rock on the seafloor may be a poisonous fish; a beautiful flower in a garden may be a carnivorous insect lying in wait for prey. This misleading appearance extends to certain components of cells, including chromosomes—the strings of linear DNA that contain the genes. At one time, the DNA at the ends of chromosomes seemed to be static. Yet in most organisms that have been studied, the tips, called telomeres, are actually ever changing; they shorten and lengthen repeatedly.

During the past 15 years, investigation of this unexpected flux has produced a number of surprising discoveries. In particular, it has led to identification of an extraordinary enzyme named telomerase that acts on telomeres and is thought to be required for the maintenance of many human cancers. This last finding has sparked much speculation that drugs able to inhibit the enzyme might combat a wide array of malignancies. The research also opens the possibility that changes in telomere length over the course of human cells.

Modern...
in the...
Uni...
Edi...
real...
stal...
"pa...
to o...
acti...



WIKIMEDIA COMMONS/NATIONAL HUMAN GENOME RESEARCH (user GIAC38)

ADVERTISEMENT

坚持一个月 听懂CNN

立即行动

上班时我也偷偷练口语, 每天只要5分钟, 30天后真的不一样!

Back to School Sale!

12 Digital Issues + 4 Years of Archive Access just \$19.99

SAVE 50%

Order Now >

its roots in experiments carried out by Barbara McClintock, then at the University of Chicago, and later by J. Muller, then at the University of Wisconsin. In many organisms, both investigators found that telomeres were present at their ends that provided stability. In the Greek for "end" (*telos*) and these end caps, chromosomes stick together and misbehave in other ways. These changes lead to the reorganization of chromosomes and, consequently, of the cells housing them.

It was not until the 1970s, however, that the precise makeup of the telomere was determined. In 1978 one of us (Blackburn), then working with Joseph G. Gall of Yale University, found that the telomeres in *Tetrahymena*, a ciliated, single-cell pond dweller, contained an extremely short, simple sequence of nucleotides—TTGGGG—repeated over and over. (Nucleotides are the building blocks of DNA;

they are generally denoted as single letters representing the chemical bases that distinguish one nucleotide from another. The base in *T* nucleotides is thymine; that in *G* nucleotides is guanine.)

Since then, scientists have characterized the telomeres in a host of creatures, including animals, plants and microorganisms. As is true of *Tetrahymena*, virtually all telomeres—including those of mice, humans and other vertebrates— contain repeated short subunits often rich in *T* and *G* nucleotides [see "The Human Telomere," by Robert K. Moyzis; SCIENTIFIC AMERICAN, August 1991]. For instance, human and mouse telomeres feature the sequence *TTAGGG*; those of roundworms feature *TTAGGC*. (*A* stands for adenine, *C* for cytosine.)

In Search of Telomerase

The telomerase enzyme that is the object of so much attention today was found when comparisons of telomere length suggested such an enzyme could resolve a long-standing puzzle in biology. By the early 1980s investigations had revealed that, for some reason, the number of repeated subunits in telomeres differs between organisms and even between different cells in the same organism. Moreover, the number can fluctuate in a given cell over time. (Every species, however, has a characteristic average. In *Tetrahymena*, the average telomere has 70 repeats; in humans, 2,000.) The observed heterogeneity led Blackburn, who had moved to the University of California at Berkeley, Jack W. Szostak of Harvard University and Janis Shampay of Berkeley to propose a new solution to what has been called the end-replication problem.

The problem has to do with the fact that cells must replicate their genes accurately whenever they divide, so that each so-called daughter cell receives a complete set. Without a full set of genes, a daughter cell may malfunction and die. (Genes are those sequences of nucleotides that give rise to proteins and RNA, the molecules that carry out most cellular functions. The genes in a chromosome are scattered throughout the large expanse of DNA that is bounded by the chromosome's two telomeres.)

In 1972 James D. Watson, working at both Harvard and Cold Spring Harbor Laboratory, noted that DNA polymerases, the enzymes that replicate DNA, could not copy linear chromosomes all the way to the tip. Hence, the replication machinery had to leave a small region at the end (a piece of the telomere) uncopied. In theory, if cells had no way to compensate for this quirk, chromosomes would shorten with each round of cell division. Eventually, the erosion would eliminate the telomeres and critical genes in some generation of the cells. These cells would thus perish, spelling the end of that cellular lineage. Clearly, all single-cell species subject to such shortening manage to counteract it, or they would have vanished long ago. So do germ-line cells (such as the precursors of sperm and eggs), which perpetuate the species in multicellular organisms. But how do such cells protect their telomeres?

For Blackburn, Szostak and Shampay, the observed fluctuations in telomere length were a sign that cells attempt to maintain telomeres at a roughly constant size. Yes, telomeres do shorten during cell division, but they are also lengthened by the attachment of newly synthesized telomeric subunits. The researchers suspected that the source of these additional repeats was some undiscovered enzyme capable of a trick that standard DNA polymerases could not perform.

When cells replicate their chromosomes, which consist of two strands of DNA twisted around each other, they begin by separating the double helix. The polymerases use each of these "parent" strands as a template for constructing a new partner. The special enzyme the workers envisioned would be able to build extensions to single strands of DNA from scratch, without benefit of an existing DNA template.

In 1984 the two of us, working in Blackburn's laboratory at Berkeley, set out to discover whether this putative telomere-lengthening enzyme—telomerase—actually existed. To our delight, we found it did. When we mixed synthetic telomeres with extracts of *Tetrahymena* cells, the telomeres gained added subunits, just as would be expected if the proposed enzyme were present.

Within the next several years we and our colleagues learned much about how telomerase works. Like all polymerases and virtually all enzymes, it consists mainly of protein, and it requires that protein to function. Uniquely, though, it also includes a single molecule of RNA (close cousin to DNA) that contains the critical nucleotide template for building telomeric subunits. Telomerase places the tip of one strand of DNA on the RNA, positioning itself so that the template lies adjacent to that tip. Then the enzyme adds one DNA nucleotide at a time until a full telomeric subunit is formed. When the subunit is complete, telomerase can attach another by sliding to the new end of the chromosome and repeating the synthetic process.

Telomerase and Human Aging

In 1988 Greider left Berkeley for Cold Spring Harbor Laboratory, and later our groups and others found telomerase in ciliates distinct from *Tetrahymena*, as well as in yeast, frogs and mice. In 1989 Gregg B. Morin of Yale also discovered it, for the first time, in a human cancer cell line—that is, in malignant cells maintained for generations in culture dishes. Today it is evident that telomerase is synthesized by nearly all organisms with nucleated cells. The precise makeup of the enzyme can differ from species to species, but each version possesses a species-specific RNA template for building telomeric repeats.

The importance of telomerase in many single-cell organisms is now indisputable. Such organisms are immortal in that, barring accidents or geneticists meddling in their lives, they can divide indefinitely. As Guo-Liang Yu in Blackburn's research group demonstrated in 1990, *Tetrahymena* needs telomerase in order to retain this immortality. When the enzyme is altered, telomeres shrink and cells die. Blackburn's team and others have similarly demonstrated in yeasts that cells lacking telomerase undergo telomere shortening and perish. But what role does telomerase play in the human body, which consists of a myriad of cell types and is considerably more complex than *Tetrahymena* or yeast?

Surprisingly, many human cells lack telomerase. Greider and others made this discovery in the late 1980s, when they pulled together the threads of research that investigators in Philadelphia had initiated more than 25 years earlier. Before the 1960s, human cells that replicated in the body were thought to be capable of dividing endlessly. But then Leonard Hayflick and his co-workers at the Wistar Institute demonstrated unequivocally that this notion was incorrect. Today it is known that somatic cells (those not part of the germ line) derived from human newborns will usually divide 80 to 90 times in culture, whereas those from a 70-year-old are likely to divide only 20 to 30 times. When human cells that are normally capable of dividing stop reproducing—or, in Hayflick's words, become "senescent"—they look different and function less efficiently than they did in youth, and after a while they die.

In the 1970s a Soviet scientist named A. M. Olovnikov linked this programmed cessation of cell division to the end-replication problem. He proposed that human somatic cells might not correct the chromosomal shortening that occurs when cells replicate their DNA. Perhaps division ceased when cells discerned that their chromosomes had become too short.

We were unaware of Olovnikov's ideas until 1988, when Calvin B. Harley, then at McMaster University, brought them to Greider's attention. Intrigued, Greider, Harley and their collaborators decided to see if chromosomes do get shorter in human cells over time.

Sure enough, most normal somatic cells they examined lost segments of their telomeres as they divided in culture, a sign that telomerase was not active. Similarly, they and Nicholas D. Hastie's group at the Medical Research Council (MRC) in Edinburgh found that telomeres in some normal human tissues shrink as people age. (Reassuringly, Howard J. Cooke, also at the MRC in Edinburgh, had shown that telomeres are kept intact in the germ line.) These results indicated that human cells might "count" divisions by tracking the number of telomeric repeats they lose, and they might stop dividing when telomeres decline to some critical length. But definitive proof for this possibility has not yet been obtained.

Could the reduction of telomeres and of proliferative capacity over time be a cause of human aging? It is probably not the main cause. After all, cells can usually divide more times than is required in a human life span. Nevertheless, the functioning of the older body may at times be compromised by the senescence of a subset of cells. For instance, local wound healing could be impaired by a reduction in the number of cells available to build new skin at a site of injury, and a reduction in the number of certain white blood cells could contribute to age-related declines in immunity. Further, it is known that atherosclerosis typically develops where blood vessel walls have been damaged. It is conceivable that cells at repeatedly injured sites could finally "use up" their replicative capacity, so that the vessels ultimately fail to replace lost cells. Then damage would persist, and atherosclerosis would set in.

The Cancer Connection

Some investigators suspect that the loss of proliferative capacity observed in human cells lacking telomerase may have evolved not to make us decrepit but to help us avoid cancer. Cancers arise when a cell acquires multiple genetic mutations that together cause the cell to escape from normal controls on replication and migration. As the cell and its offspring multiply uncontrollably, they can invade and damage nearby tissue. Some may also break away and travel to parts of the body where they do not belong, establishing new malignancies (metastases) at distant sites. In theory, a lack of telomerase would retard the growth of tumors by causing continually dividing cells to lose their telomeres and to succumb before they did much damage. If cancer cells made telomerase, they would retain their telomeres and would potentially survive indefinitely.

The notion that telomerase might be important to the maintenance of human cancers was discussed as early as 1990. But the evidence did not become compelling until recently. In 1994 Christopher M. Counter, Silvia Bacchetti, Harley and their colleagues at McMaster showed that telomerase was active not only in cancer-cell lines maintained in the laboratory but in ovarian tumors in the human body. Later that year groups led by Harley, who had moved to Geron Corporation in Menlo Park, Calif., and by Jerry W. Shay of the University of Texas Southwestern Medical Center at Dallas detected telomerase in 90 of 101 human tumor samples (representing 12 tumor types) and in none of 50 samples of normal somatic tissue (representing four tissue types).

Even before such evidence was obtained, however, researchers had begun exploring some of the details of how telomerase might contribute to cancer. That work suggests telomerase probably becomes active after a cell has already lost its brakes on proliferation.

The first clue was an initially mystifying discovery made independently by Titia de Lange, now at the Rockefeller University, and by Hastie's group. In 1990 these investigators reported that telomeres in human tumors were shorter than telomeres in the normal

surrounding tissue—sometimes dramatically so.

Studies by Greider's, Bacchetti's and Harley's laboratories explained why the telomeres were so small. The teams had induced normal cells from humans to make a viral protein causing cells to ignore the alarm signals that usually warn them to stop dividing. The treated cells continued to proliferate long after they would normally enter senescence. In most of the cells, telomeres shortened drastically, and no telomerase was detected; eventually death ensued. Some cells, however, persisted after their siblings died and became immortal. In these immortal survivors, telomeres were maintained at a strikingly short length, and telomerase was present.

These outcomes imply that telomeres in cancer cells are small because cells synthesize telomerase only after they have already begun to replicate uncontrollably; by then, the cells have presumably lost a substantial number of telomeric subunits. When the enzyme is finally activated, it stabilizes the severely clipped telomeres, allowing overly prolific cells to become immortal.

These findings and others have led to an attractive but still hypothetical model for the normal and malignant activation of telomerase by the human body. According to this model, telomerase is made routinely by cells of the germ line in the developing embryo. Once the body is fully formed, however, telomerase is repressed in many somatic cells, and telomeres shorten as such cells reproduce. When telomeres decline to a threshold level, a signal is emitted that prevents the cells from dividing further.

If, however, cancer-promoting genetic mutations block issuance of such safety signals or allow cells to ignore them, cells will bypass normal senescence and continue to divide. They will also presumably continue to lose telomeric sequences and to undergo chromosomal alterations that allow further, possibly carcinogenic mutations to arise. When telomeres are completely or almost completely lost, cells may reach a point at which they crash and die.

But if the genetic derangements of the pre-crisis period lead to the manufacture of telomerase, cells will not completely lose their telomeres. Instead the shortened telomeres will be rescued and maintained. In this way, the genetically disturbed cells will gain the immortality characteristic of cancer.

This scenario has generally been borne out by the evidence, although, once again, things may not be entirely as they seem. Some advanced tumors lack telomerase, and some somatic cells—notably the white blood cells known as macrophages and lymphocytes—have recently been found to make the enzyme. Nevertheless, on balance, the collected evidence suggests that many tumor cells require telomerase in order to divide indefinitely.

Prospects for Cancer Therapy

The presence of telomerase in various human cancers and its absence in many normal cells mean the enzyme might serve as a good target for anticancer drugs. Agents able to hobble telomerase might kill tumor cells (by allowing telomeres to shrink and disappear) without disrupting the functioning of many normal cells. In contrast, most existing anticancer therapies disturb normal cells as well as malignant ones and so are often quite toxic. Further, because telomerase occurs in numerous cancers, such agents might work against a broad array of tumors.

These exciting possibilities are now being actively explored by pharmaceutical and biotechnology companies. Nevertheless, a number of questions must be answered. For instance, researchers need to determine which normal cells (beyond the few already identified) make telomerase, and they need to assess the importance of the enzyme to those cells. If telomerase is crucial, drugs that interfere with it might in fact prove unacceptably toxic. The shortness of telomeres in certain tumor cells may obviate this problem, however. Telomerase-inhibiting agents might cause cancer cells to lose their telomeres and die well before normal cells, with their much longer telomeres, lose enough of their telomeres to suffer any ill effects.

Investigators must also demonstrate that inhibition of telomerase can destroy telomerase-producing tumors as expected. Last September, Harley, Greider and their co-workers showed that an inhibitory agent could cause the telomeres of cultured tumor cells to shrink; the affected cells died after about 25 cycles of cell division. Blackburn, now at the University of California at San Francisco, and her group have found, however, that cells sometimes compensate for the loss of telomerase. They repair their shortened ends by other means, such as by a process called recombination, in which one chromosome obtains DNA from another. If activation of alternative, "telomere-salvaging" pathways occurs frequently in human tumors, therapy targeted to telomerase would fail.

Studies of animals should help resolve such concerns. They should also help reveal whether inhibitors of telomerase will eliminate tumors in the living body and whether they will do so quickly enough to prevent cancers from injuring critical tissue.

To develop agents that will block telomerase in the human body, investigators must also have a sharper picture of exactly how the enzyme functions. How does it attach to DNA? How does it "decide" on the number of telomeric subunits to add? DNA in the nucleus is studded with all manner of proteins, including some that specifically bind to the telomere. What part do telomere-binding proteins play in

controlling the activity of telomerase? Would altering their activity disrupt telomere elongation? Within the next 10 years we expect to learn a great deal about the interactions among the various molecules that influence telomere length.

Research into the regulation of telomere size could also yield benefits beyond new therapies for cancer. A popular approach to gene therapy for various diseases involves extracting cells from a patient, inserting the desired gene and then returning the genetically corrected cells to the patient. Frequently, though, the extracted cells proliferate poorly in the laboratory. Perhaps insertion of telomerase alone or in combination with other factors would temporarily enhance replication capacity, so that larger numbers of therapeutic cells could be delivered to the patient.

Modern research into telomeres has come a long way from the initial identification of repetitive DNA on the ends of chromosomes in a unicellular pond dweller. Elongation of telomeres by telomerase, initially considered to be merely a "cute" mechanism by which some single-cell creatures maintain their chromosomes, has proved, as ever, to be other than it seemed. Telomerase is, in fact, the predominant means by which nucleated cells of most animals protect their chromosomal end segments. And, now, study of this once obscure process may lead to innovative strategies for fighting a range of cancers.


In the early 1980s scientists would not have set out to identify potential anticancer therapies by studying chromosome maintenance in *Tetrahymena*. The research on telomerase reminds us that in studies of nature one can never predict when and where fundamental processes will be uncovered. You never know when a rock you find will turn out to be a gem.

ABOUT THE AUTHOR(S)

CAROL W. GREIDER and ELIZABETH H. BLACKBURN began collaborating in 1983, when Greider joined Blackburn's laboratory at the University of California, Berkeley. Greider, who earned her PhD in molecular biology from U.C. Berkeley in 1987, is senior staff scientist at Cold Spring Harbor Laboratory. Blackburn holds a 1975 doctorate in molecular biology from the University of Cambridge. She has been a professor of microbiology and immunology at the University of California, San Francisco, since 1990 and department chair since 1993.

Scientific American is a trademark of Scientific American, Inc., used with permission
 © 2014 Scientific American, a Division of Nature America, Inc.
 All Rights Reserved.

TRY A RISK-FREE ISSUE



YES! Send me a free issue of Scientific American with no obligation to continue the subscription. If I like it, I will be billed for the one-year subscription.

[Subscribe Now](#)