NOBEL PRIZE IN SCIENCES–2009

Archana Sharma

Junior Project Fellow
Department of Education in Science and Mathematics
National Council of Educational Research and Training, New Delhi

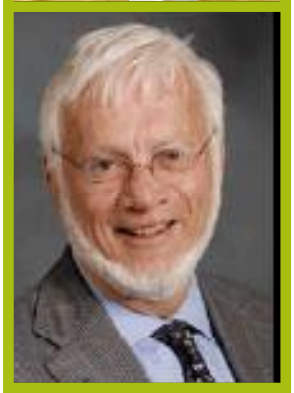
The prestigious Nobel award, instituted at the behest of the great scientist and the inventor of dynamite 'Alfred Nobel,' is tribute to persons who render most valuable service to humanity by their resolute and concerted work in different fields of physics, chemistry, physiology and medicine, economics and peace. The award is more than a mere symbol of recognition. The prize money of 1,66,000 US dollars is also of substantial help to individual scientists to carry forward research in their field of interest to satisfy their insatiable desire, in knowing the unknown for the benefit of mankind for which they have devoted their lives and effort. The Nobel Prize is an international award administered by the Nobel Foundation in Stockholm, Sweden.

Like every year, the Nobel Prize for physics and chemistry for the year 2009 were announced by the Swedish Academy of Science while The Stockholm Faculty of Medicine recommended the awards for physiology and medicine.

Nobel Prize in Chemistry

This year's Nobel Prize in Chemistry has been awarded to three scientists: Venkatraman Ramakrishnan, Thomas A. Steitz, and Ada E. Yonath for enlightening the science community on the 'structure and function of the ribosome'. Out of the three big molecules for life (DNA, RNA, and Proteins), proteins arguably take lion's share of the work. Proteins provide structural stability to the cells, give mechanical motion to muscles, transport oxygen and play many other key role in nearly every chemical reaction that occurs in the cells. The three Nobel awardees, Ramakrishnan, Steitz, and Yonath, used- X-ray crystallography to identify and map the positions of the atoms in the ribosome to provide its 3-D models to scientists to facilitate further studies and dissect them for crucial information at the atomic level. This was a unique achievement as there are hundreds of thousands of atoms involved. Their work has benefited many other areas of research, including the study of antibiotics. As synthesis of proteins is essential for the survival of bacteria, the ribosome is a practical target for drugs. The researches carried out by Nobel laurates have provided vital information for the design of new antibiotics. The three-dimensional model (3-D), developed by the three scientists showed how different antibiotics bind to ribosomes. These models are now used by scientists in order to develop new antibiotics, directly assisting the saving of lives and decreasing humanity's suffering.

Venkatraman Ramakrishnan



Thomas A. Steitz

Ada E. Yonath

Fig. 1 : Nobel Prize awardees in Chemistry

Venkatraman Ramakrishnan, born in 1952 in Tamil Nadu, India, did his Ph.D from University of Ohio in 1976. He is a senior scientist and now leads a strong research group at the Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge, UK. He has determined the structure of the *Thermus thermophilus's* (heat-stable bacterium) 30S ribosomal subunit in complex with several antibiotics. Dr Ramakrishnan's research into the ribosome and its complexes with antibiotics, initiation factor 1 (IF1), as well as cognate and near-cognate tRNA has resulted in an extensive body of publications.

Thomas A. Steitz, born in 1940 in Milwaukee, WI, did his Ph.D from Harvard University in 1966. He is now Sterling Professor of Molecular Biophysics and Biochemistry, and an investigator of the Howard Hughes Medical Institute. His scientific career has been focused on studying the structural basis of the molecular and chemical mechanisms by which proteins and nucleic acids execute their biological functions. Dr Steitz's imaged the first high-resolution crystal structure of the large ribosomal subunit known as 50s from *Haloarcula marismortui* with a resolution of 9 Å.

Ada E. Yonath, born in 1939 in Jerusalem, Israel, did her Ph.D in X-ray Crystallography from Weizmann Institute, Israel in 1968. She is presently the Director of the Kimmelman Centre for Biomolecular Assemblies at the Weizmann Institute of Science in Rehovot, Israel. The ribosome was central to her research from the initial crystallisation studies in the late 1970s to her first electron density map of the small ribosomal subunit from *Thermus thermophilus*, constructed at 4.5 Å.

Yonath and Ramakrishnan obtained the structure of the small subunit (30S) from *Thermus thermophilus*. Thus, it was possible to map ribosome functionality at the most basic, atomic level.

Their research showed how the ribosome looks like and how it functions at the atomic level. They have used a method called X-ray crystallography to map the position of every one of the hundreds of thousands of atoms that make up the ribosome. This method determines the three dimensional structure of molecules which are organised in different pattern in the crystals. These molecules within the crystal diffract the X-rays in specific directions when these are exposed to a beam of X-rays. By studying the diffraction pattern, the intensities and position of the diffracted beam, crystallographers can identify the position and atomic details of the molecules.

By building a (3-D) structure of the ribosome using X-ray crystallography method, they solved an important part of the problem posed by Francis Crick and James Watson, when they proposed the twisted double helical structure of DNA, i.e. how does genetic code become a living thing? DNA is made available to the ribosome by "transcription" of genes into chunks of messenger RNA (mRNA). In the ribosome, these mRNA are translated into various amino acid sequences by the method of translation and make up an organism's proteins. The work is based on a technique called X-ray crystallography, where protein molecules are removed from cells, purified and made into crystals that can be examined by X-rays.

Every cell of the organism have DNA molecules in their nucleus. They contain the blueprints for how an organism, say a human being, a plant or a bacterium, looks and functions. These blueprints get transformed into living matter through the function of ribosomes. Based upon the information coded in DNA, proteins are formed in ribosomes. There are tens of thousands of proteins in the body of an organism and they have different structures and functions. They build and control life at the chemical level.

Ribosomes were first discovered in the mid 1950s by a cell biologist George Palade using electron microscope and the term 'ribosome' for them was proposed by Biologist Richard B.

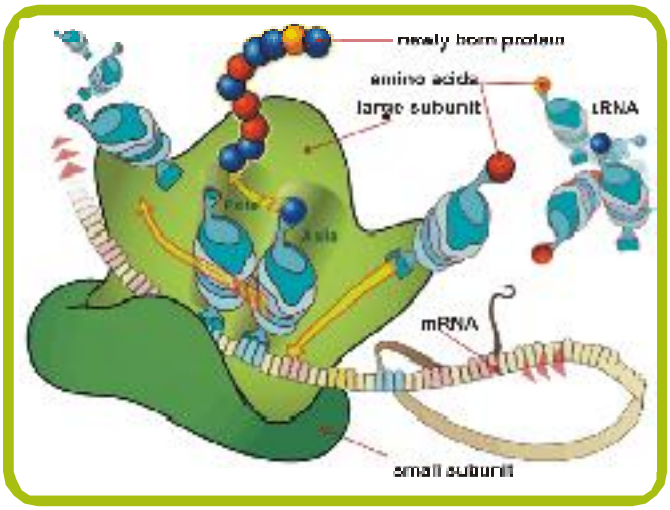


Fig. 2: Translation Process (the synthesis of protein)

(Source : http://www.ortodoxiatinerilor.ro/2008/09/genele-sinteza-proteinelor-codul-genetic-5)

Roberts. An understanding of structure and function of the ribosome is important for a scientific understanding of life. Ribosome is the part of cellular components that makethe protein. It is
20 nm in diametre and is made up of a complex comprising 65 per cent RNAsand 35per cent Protein. Ribosomes are divided into two sub-units: larger and smaller. The unit of measurement of sub-unit is Svedberg unit (s), a measure of the rate of sedimentation in centrifugation. The ribosome is the site of protein synthesis (protein factory) in a living cell. The ribosome translates genetic code into proteins, which are the building blocks of all living organisms. The sub-unit of ribosome in prokaryotes and eukaryotes are different, the prokaryotes have 70S ribosome made up of larger sub-unit of 50S and smaller sub-unit of 30S. Eukaryoteshave 80S ribosome, ithas larger sub-unit of 60S and smaller sub-unit of 40S. These sub-units play an important role in translation, a process for the synthesis of protein. The three nucleotide genetic codon bind to these sub-unit with the help of tRNA and make the protein in this process.

Human and bacterial ribosomes are slightly different, making the ribosome a good target for antibiotic therapy that works by blocking the bacterium's ability to make the proteins it needs to function. Nowadays, various antibiotics are in use that cure diseases by blocking the function of bacterial metabolic activity in the translation process (protein synthesis). Dr Ramakrishnan discovered the function of these ribosomal sub-units complex with various antibiotics. He also determined that how antibiotics bind to specific pockets in the ribosome structure. The antibiotics cure the disease by interfering in the function of bacterial (infecting) ribosomes by preventing them to make the proteins they need to survive. As making proteins is essential for the survival of bacteria, ribosome in them is the main target of antibiotics, which stops the protein synthesis. Without functional ribosomes, bacteria cannot survive because of its inability to synthesise protein. This is why ribosome is such an important target for new antibiotics. This research could help scientiststo design antibiotics to treat people who are infected with a bacterium that has developedresistance against traditional antibiotics. Better targeting of the bacterial ribosome should also help to avoid negative effects on human cells thereby reducing the side effects of taking antibiotics. Biologists in pharmaceutical and biotechnology companies will also use this valuable information to develop new antibiotics to fight the growing problem of bacterial drug resistance.

Nobel Prize in Physics

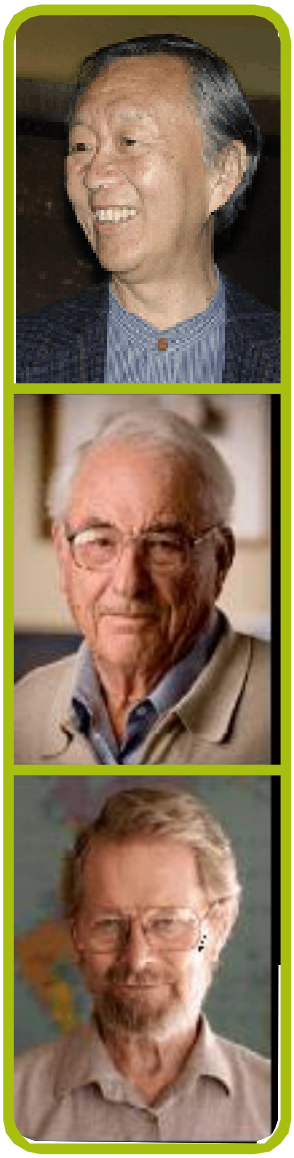
The Nobel Prize in Physics–2009 has been awarded jointly to three Scientists– Charles K. Kao, Willard S. Boyle, and George E. Smith. This year's Nobel Prize in Physics is awarded for two scientific achievements that have helpedto shape the foundations of today's networked societies. Charles K. Kao received the award for his "groundbreaking achievements concerning the transmission of light in fibres for optical communication" while Makoto Kobayashi and Toshihide Maskawa were nominated for the "invention of an imaging semiconductor circuit – the CCD sensor ".

Charles K Kao, born in 1933 in Shanghai, China, is also known as Father of Modern Communications. He did his Ph.D from University of London in 1965. He is retired Director of Engineering at Standard Telecommunication Laboratories, Harlow, UK and Vice-Chancellor at Chinese University of Hong Kong. He was cited for his 1966 discovery that showed how to transmit light over long distances via fibre-optic cables, which became the backbone of modern communication networks that carry phone calls and high-speed Internet data around the world.

Willard S. Boyle, born in 1924 in Nova Scotia, Canada, did his Ph.D from McGill University in 1950. He was Executive Director of Communication Sciences Division, Bell Laboratories, Murray Hill, New Jersey, USA. In 1962, he worked with Dr Nelson and invented the first continuously operating ruby laser; he was appointed as director of Bellcomm's (a Bell Labs subsidiary) Space Science and Exploratory Studies programme. He returned to Bell Labs in 1964. In 1969, he worked with George E. Smith to develop Charge-Coupled Devices (CCDs).

George Elwood Smith, born in 1930 in White Plains, New York, did his Ph.D from University of Chicago in 1959. He is retired Head of VLSI Device Department, Bell Laboratories, Murray Hill, USA. He was involved in a variety of investigations on junction lasers, semiconducting ferroelectrics, electroluminescence, transition-metal oxides, the silicon-diode-array camera tube, and Charge Coupled Devices (CCDs).

Boyle and Smith jointly invented the first successful imaging technology using a digital sensor, a Charge Coupled Device (CCD).



Charles K. Kao

Willard S. Boyle

George E. Smith

Fig. 3: Nobel Prize awardees in Physics

Fig. 4: Optical Fibres

(Source : ocw.mit.edu/.../detail/fibre_optics_hom.htm)

The CCD uses semiconductors, the same kind of materials as computer chips, to capture light and turn it into an electric signal. The CCD is the electronic eye of digital camera. The invention has revolutionised photography, as light could now be captured electronically instead of on films. The digital form facilitates the processing and distribution of these images. The CCD allowed whole two-dimensional fields of optical data to be read out more quickly and efficiently. The CCD has been the backbone of the commercial digital camera industry.

The CCD technology makes use of the photoelectric effect, as theorised by Albert Einstein and for which he was awarded the Nobel Prize in the year 1921. By this effect, light is transformed into electric signals. The challenge when designing an image sensor was to gather and read out the signals in a large number of image points, pixels, in a short time. Digital photography has become an irreplaceable tool in many fields of research. The CCD has provided new possibilities to visualise the previously unseen. It has given us crystal clear images of distant places in our universe as well as the depths of the oceans. The CCD contains a silicon chip that is divided into cells or "pixels". When light hits a pixel, it excites an electric charge in the silicon, which then induces a charge in a tiny electrode on the surface of the chip. The charge then quickly passes from electrode to electrode down a whole row of pixels known as "charge coupling" and is read out at the edge of the chip. The CCD technology is also used in many medical applications, e.g. for imaging the inside of the human body, both for diagnostics and for microsurgery.

Today optical fibres make up the circulatory system that nourishes our communication society. These low-loss glass fibres facilitate global broadband communication such as the Internet. Light flows in thin threads of glass, and it carries almost all of the telephony and data traffic in each and every direction. Music, video, Text and images can be transferred around the globe in a split second. Dr Kao carefully calculated how to transmit light over long distances via optical glass fibres. With a fibre of purest glass it would be possible to transmit light signals over 100 kilometres, compared to only 20 metres for the fibres available previously. His passion inspired other researchers to share his vision of the future potential of fibre optics. The first ultrapure fibre was successfully fabricated in 1970. This is one of the main technologies in modern photography. It makes the capture and reading of light fast and efficient and it essentially made photographic film obsolete, the cost of capturing an image went down to literally zero. It is also one of the standard technologies for investigation in astrophysics and

most importantly, it is not restricted to the visible spectrum. This mode of communication is essential for high speed internet and forms the optical backbone of 21st century commerce.

Nobel Prize in Physiology and Medicine

This year's Nobel Prize for physiology and medicine is shared by three scientists: Elizabeth H. Blackburn, Carol W. Greider, and Jack W. Szostak for their discovery "how chromosomes are protected by telomeres and the telomerase enzyme".

Elizabeth H. Blackburn was born on 26 November 1948 in Hobart, Tasmania. She is an Australian born U.S. biologist and done her Ph.D. at University of California, San Francisco (UCSF), she studied telomere, a structure at the end of chromosomes which protects the chromosome.

Born in 1961 at San Diego, California, Carol W. Greider completed her Ph.D. in molecular biology in 1987 at the University of California, Berkeley, under Elizabeth Blackburn. Presently, she is a Professor and Director of Molecular Biology and Genetics at the John Hopkins Institute of Basic Biomedical Sciences. She discovered the enzyme telomerase in 1984 while working with Elizabeth Blackburn. She pioneered research on the structure of telomeres, the ends of chromosomes.

Jack W. Szostak was born on 9 November 1952 in London. He completed his Ph.D. from Cornell University (US). Presently, he is a biologist and Professor of Genetics at Harvard Medical School and Alexander Rich Distinguished Investigator at Massachusetts General Hospital, Boston. He is

Fig. 5: Nobel Prize awardees in Physiology and Medicine

Elizabeth H. Blackburn

Carol W. Greider

Jack W. Szostak

credited with the construction of the world's first yeast artificial chromosome. This construction helped him to map the location of gene in mammals which played a pivotal role in Human Genome Project. Dr Szostak's discoveries have paved the way to clarify the events that lead to chromosomal recombination, the reshuffling of genes that occurs during meiosis and also to unravel the function of telomere gene.

(1952-11-09) The DNA of all organisms (whether prokaryotic or eukaryotic) multiply (get divided) by a process called DNA Replication, such that the newly formed strand of DNA is the exact copy of its parent DNA. The replication process is different in prokaryotes and eukaryotes. In prokaryotes the circular DNA replication is terminated by Ter (terminus)-Tus (terminus utilisation sequences) complex sequences. But termination of linear eukaryotic chromosome involves the synthesis of special structure, called telomeres chromosome, present at the end of all eukaryotic chromosome. Telomeres consist of tandem repetitive arrays of the hexameric sequence TTAGGG and play an important protective role in the cells. Their presence on the tips of chromosomes prevents important genetic material from being lost during cell division. The overall size of telomere is ranging from ~15 Kilobase (kb) at birth sometimes 55 kb in chronic disease states. The telomeric repeats help maintain chromosomal integrity and provide a buffer of potentially expendable DNA. The ends of telomeres are protected and regulated by telomere-binding proteins and form a special lariat-like structure called the t-loop. This packaging or protective cap at the end of linear chromosomes is thought to mask telomeres from being recognised as broken or DNA damage, thus

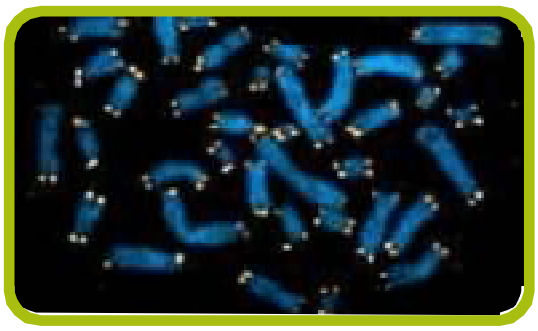


Fig. 6: Chromosome and Telomeric DNA

(Source : physics.berkeley.edu/.../yildiz/Research.html)

protecting chromosome termini from degradation, recombination and end-joining reactions.

Fig 6 depicts the chromosome in blue colour and the white point like structure present at the tip of chromosome is the telomeric DNA.

The inability of DNA polymerase to replicate the end of the chromosome during lagging strand synthesis ('end replication problem') coupled with possible processing events in both leading and lagging daughters, results in the loss of telomeric repeats each time a cell divides and ultimately leads to replicative senescence. This problem is solved by the 'Telomerase enzyme'. The telomerase is a ribonucleoprotein enzyme essential for the replication of chromosome termini in eukaryotes. It is an essential enzyme that maintains telomeres on eukaryotic chromosomes. The importance of telomeres was first elucidated in plants 60 years ago. Little is known about the role of telomeres and telomerase in plant growth and development. enzyme adding telomeric repeats onto the 32 This

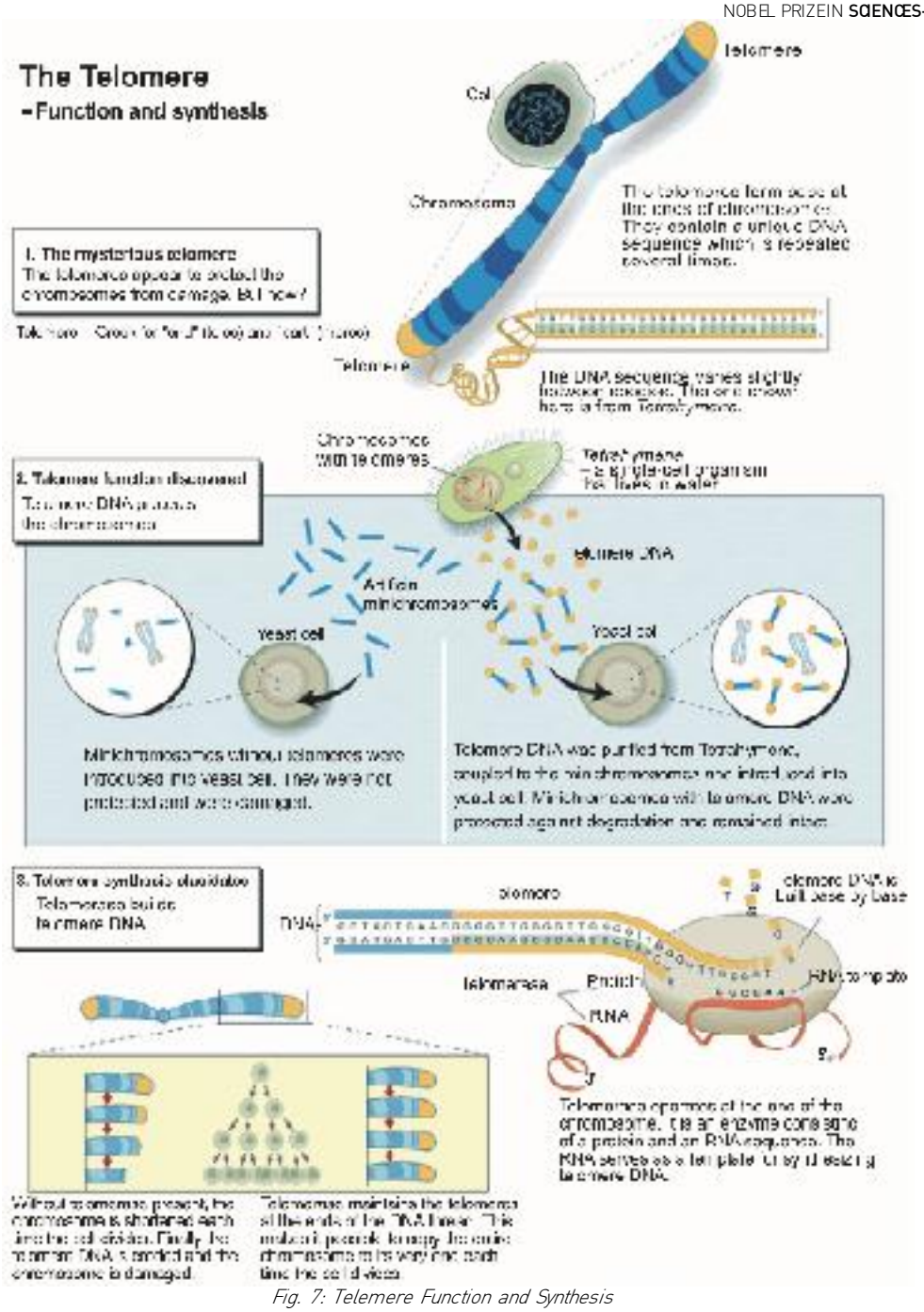


Fig. 7: Telemere Function and Synthesis

Source : www.highlight health.com/.../2009/10/telomere.gif

ends (3 prime ends) of the DNA limits. Telomerase act like a cellular reverse transcriptase enzyme, which is RNA dependent DNA synthesis. The enzyme telomerase, which builds telomeres, enables the entire length of the chromosome to be copied without missing the end portion.

Telomerase uses its integral RNA component as a template in order to synthesise telomeric DNA (TTAGGG)n, directly onto the ends of chromosomes. After adding six bases, the enzyme pauses while it repositions (translocates) the template RNA for the synthesis of the next 6 bp repeat. This extension of the 32 DNA template eventually permits additional replication of the C-rich strand, thus compensating for the end-replication problem. Average telomere length, gives some indication of how many divisions the cell has already undergone and how many remain before it can no longer replicate.

All telomeres have the same short sequence of DNA bases repeated thousands of times. Rather than containing any genetic information, these repetitive snippets help keep chromosomes intact. Short telomeres are more common in older cells; telomere capping problems may be related to the development of age-related diseases. Telomerase expression is also detected in a majority of cancers, but is absent in most somatic tissues and correlates to clinical outcome in a number of cancer types. Cancer and aging research merge in the study of telomeres. The tails at the ends of chromosomes that become shorter as a cell divides, is defected in cancer cells. It divides continuously as cancer cell has uncontrolled growth regulatory system.

Role of Telomere and Telomerase in Cancer

In cancer cells, telomeres act abnormally; they no longer shorten with each cell division. Healthy human cells are mortal because they can divide only a finite number of times, growing older each time they divide. It has been proposed that telomere shortening may be a molecular clock mechanism that counts the number of times a cell has divided and when telomeres are short, cellular senescence (growth arrest) occurs.

The cancer cell has uncontrolled growth regulatory system as it divides beyond the normal limits. Telomerase is an enzyme that "rewinds" the mitotic or cellular clocks. Telomerase strengthens and lengthens the shortened telomeres in the cells, replacing the bits of DNA lost in normal cell division. If telomerase stops telomere shortening, those cells with telomerase can live forever. Since most cancer cells contain telomerase, researchers believe it is a critical factor in conferring immortality upon these cells.

Dr Blackburn and Dr Greider discovered the enzyme telomerase, which is not active in most adult cells but becomes active in advanced cancers, enabling cells to replace lost telomeric sequences and divide indefinitely. Their discovery therefore, might aid in cancer treatment. Lots of work is going on cancer which is related to telomerase enzyme. If the telomerase activity in the cancer cell stops or reduces then it is easy to cure to some extent the cancer in persons. Telomerase expression is associated with the stage of differentiation but not necessarily with

the rate of cell proliferation. The inhibition or absence of telomerase may result in cell crisis in cancer cells and tumor regression in cancer patients. These results suggest that cancer therapy based on telomerase inhibition could be a more effective and safer treatment for cancer; it could as well provide a more accurate means for diagnosing and predicting clinical outcome in cancer. In addition, some inherited diseases are now known to be caused by telomerase defects, including certain forms of congenital aplastic anemia, and some inherited skin and lung diseases.

Role of Telomere and Telomerase in Aging

Natural aging involves the telomeres, which over time lose their ability to replicate as frequently as when they were younger. Aging is a progressive decline in vitality over time leading to death. It is a side product of metabolism. The process of cell division is called mitosis. Each time mitosis occurs, the telomeres of the dividing cells get just a bit shorter. Once a cell's telomeres have reached a critically short length, that cell can no longer divide. Its structure and function begins to fail, and some cells even die. The telomere hypothesis of aging postulates that as the telomeres naturally shorten during the lifetime of an individual, a signal or set of signals is given to the cells to cause the cells to cease growing (senesce). According to, Dr Langmore, at birth, human telomeres are about 10,000 base pairs long, but by 100 years of age this has been reduced to about 5,000 base pairs. Many scientists speculated that telomere shortening could be the reason for aging, not only in the individual cells but also in the organism as a whole. But the aging process has turned out to be complex and it is now thought to depend on several different factors, the telomere being one of them. In the absence of telomerase, the telomere will become shorter after each cell division. When it reaches a certain length, the cell may cease to divide and they die. Therefore, telomerase plays an essential role in the aging process. There is little evidence that commonly observed changes in older individuals, such as anemia and impaired wound healing, result from impaired cellular proliferation, which would be the anticipated consequence of shortened telomeres. Despite the lack of clear evidence for impaired proliferation in aging there is, in fact, good evidence for progressive telomere shortening in many human cell types, including peripheral white blood cells, smooth muscle cells, endothelial cells, lens epithelial cells, muscle satellite cells, and adrenocortical cells, etc. The proliferative capacity is closely related to telomere length in endothelial cells. Telomere lengths in endothelial cells decreases as a function of donor age, with a greater decline being observed in cells isolated from the iliac artery. The greater decline in telomere length was observed in the cells that have likely undergone more proliferation *in vivo*, because they resided in a part of the vascular system where blood flow might cause most chronic damage to the endothelium.

The discoveries of the Nobel laureates has added a new dimension to the scientific community's understanding of the cell, shed light on disease mechanisms, and introduced new directions for the development of potential new therapies.

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