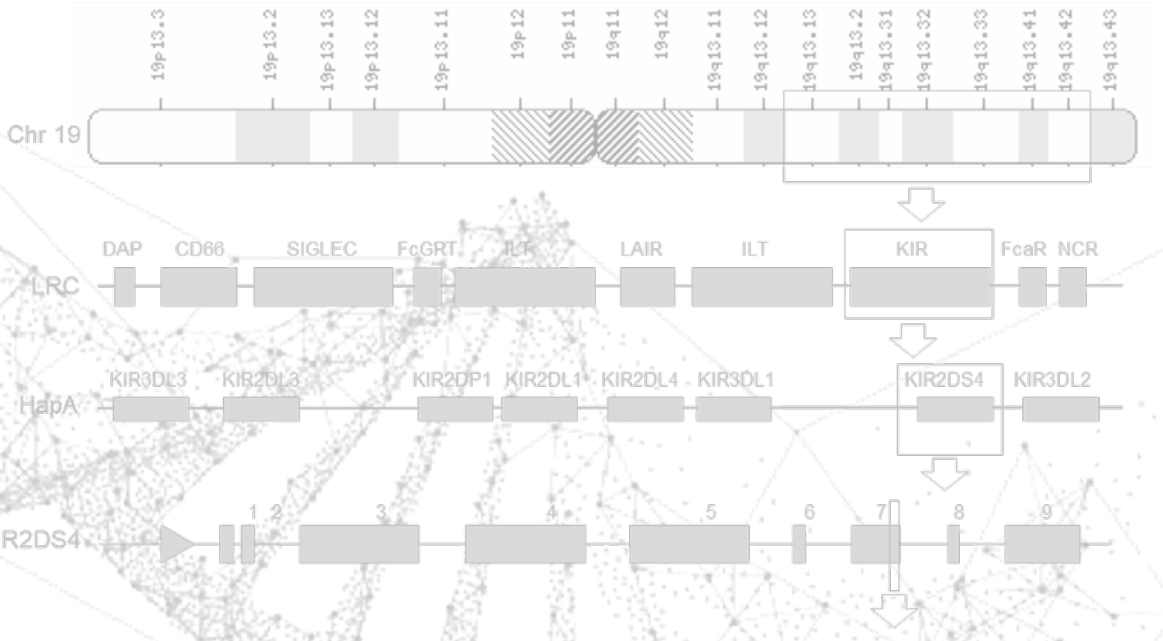


Genomic Compaction in Eukaryotes

San Luis Potosi State University (UASLP) Mexico
Molecular Biology Course, Faculty of Medicine post-graduate program

Dr. Christian A. García-Sepúlveda

Viral & Human Genomics BSL-3 Laboratory

Last updated October 21, 2024 v1

Eukaryote genome compaction overview

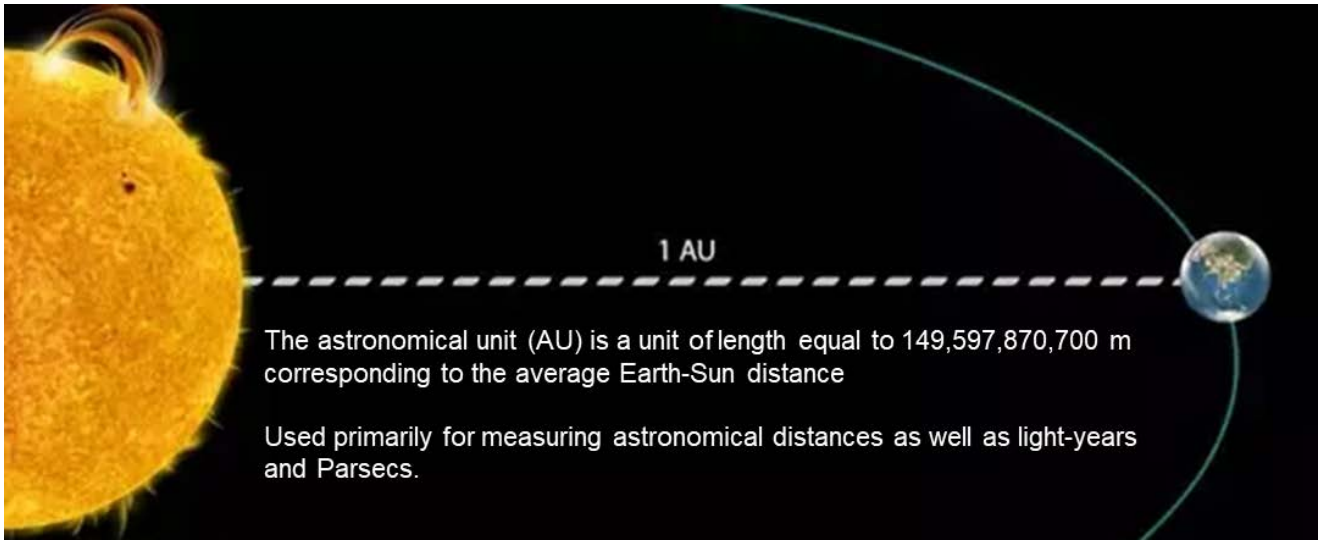
Length of a single base pair: 0.34 nm

Base content per haplotype: 3 billion (thousands of millions) bp

Net haplotype length: 1.02 meters

Net genome length (2n): 2 meters

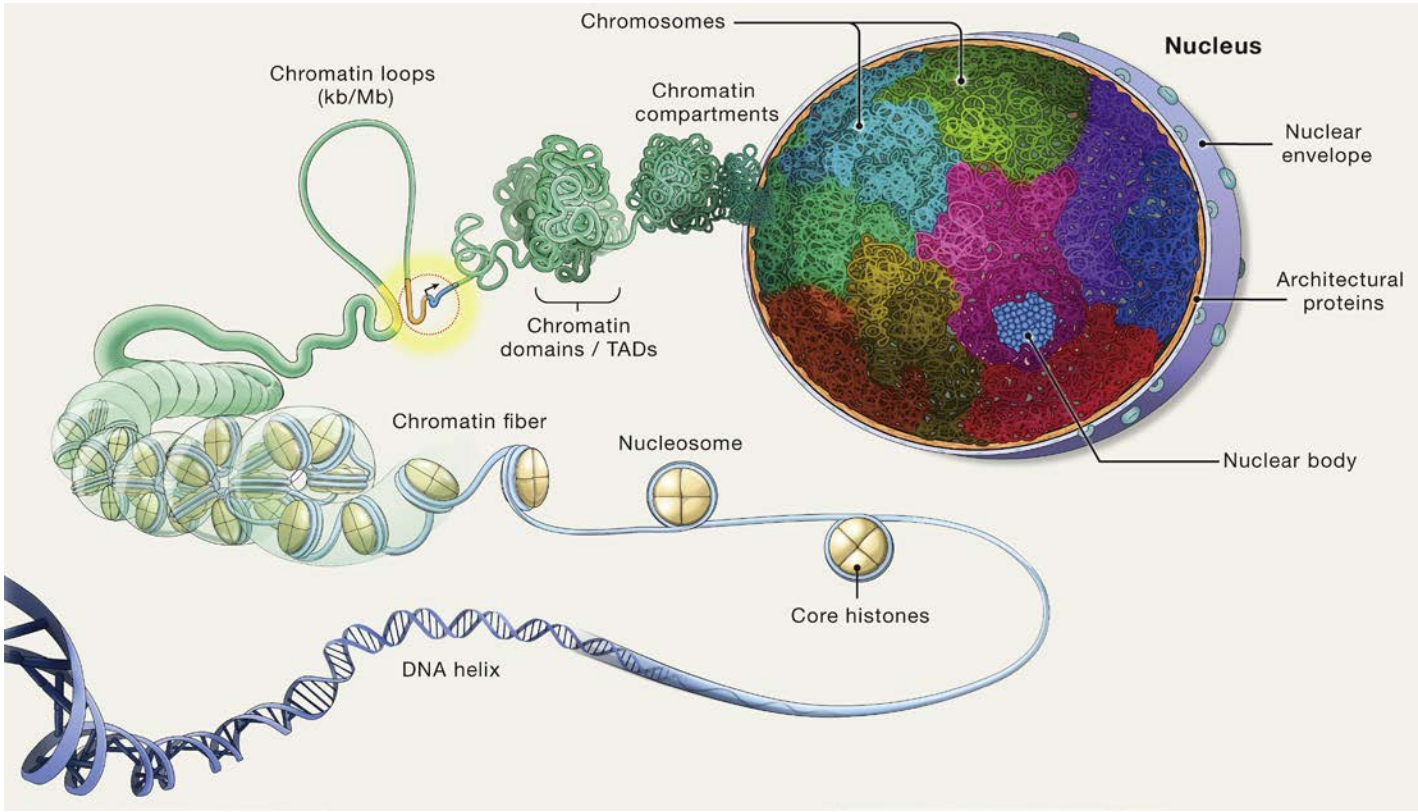
As the human body has ~37 trillion cells, the combined length of DNA in a person would stretch to the sun and back multiple times!



Eukaryote genome compaction overview

Eukaryotic genomes are organized into several architectural features.

The basic organizational hierarchies are 10 nm fibres, 30 nm fibres, 300 nm loops, chromatin domains, topologically associating domains, chromatin compartments and chromosomes.



Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Nucleosome (10 nm chromatin fiber)

The basic structural unit of DNA packaging common to all eukaryotes.

carry epigenetically inherited information in the form of covalent modifications of their core histones.

1.67 turns of DNA (146 bp in HoSa).

50 to 80 bp linker DNA.

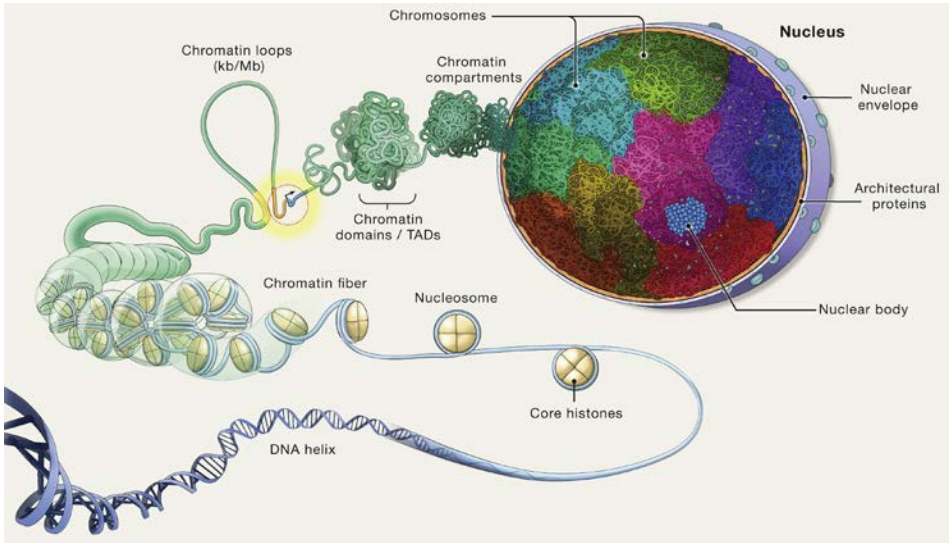
Histone octamer is 6 x 11 nm in dimensions.

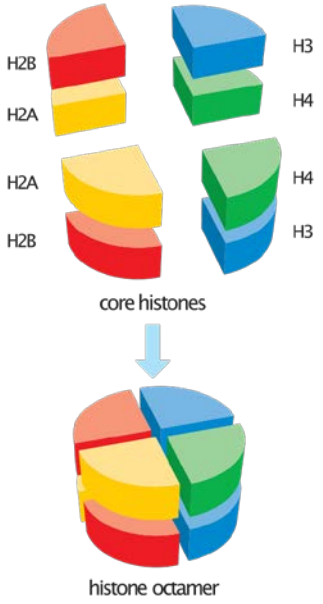
H1 at the base of the nucleosome seals DNA entry and exit.

Histone equivalents found in Archae.

Beads-on-a-string structure (10 nm fiber).

Chromatin, a combination of DNA and histone proteins.





30 nm chomratin fiber

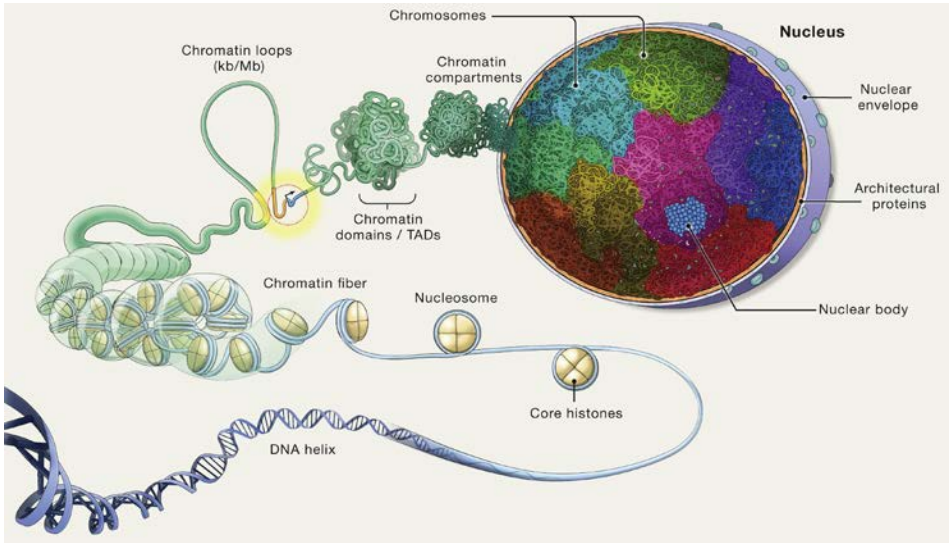
Consists of nucleosomes coiled into a solenoid or zigzag arrangement.

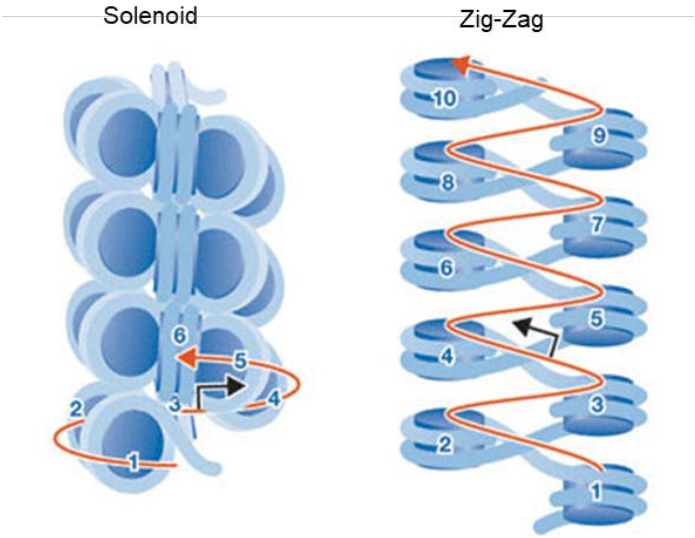
In the solenoid model, nucleosomes form a spiral, with about 6 nucleosomes per turn.

In the zigzag model, the nucleosomes are arranged in a back-and-forth pattern, with linker DNA connecting them.

Reduces DNA length by around 50-fold.

Not a static structure; it is dynamic and can undergo loosening or tightening based on chromatin remodelling, gene expression needs, or cell cycle stages.





Chromatin loops

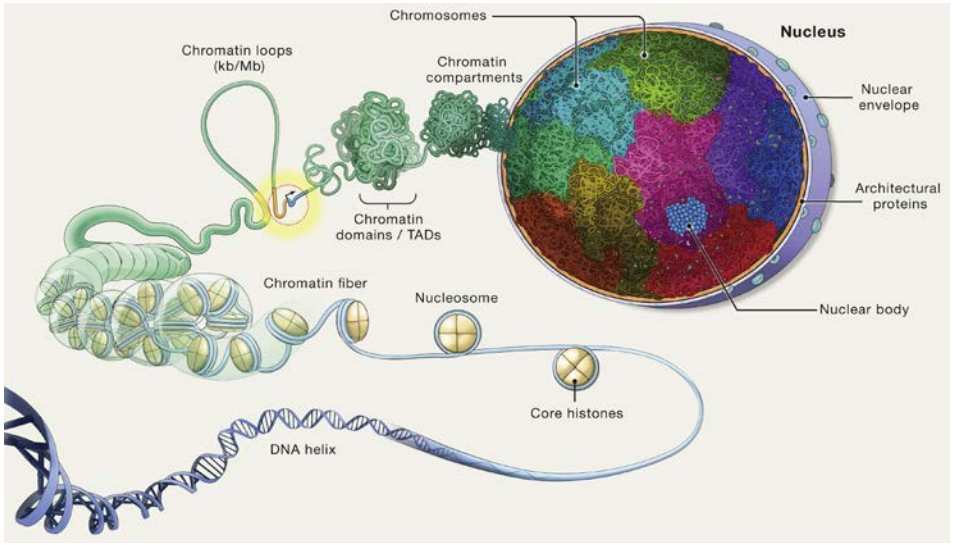
Formed by the folding of the 30 nm chromatin fiber into looped structures, which are anchored to a structural framework.

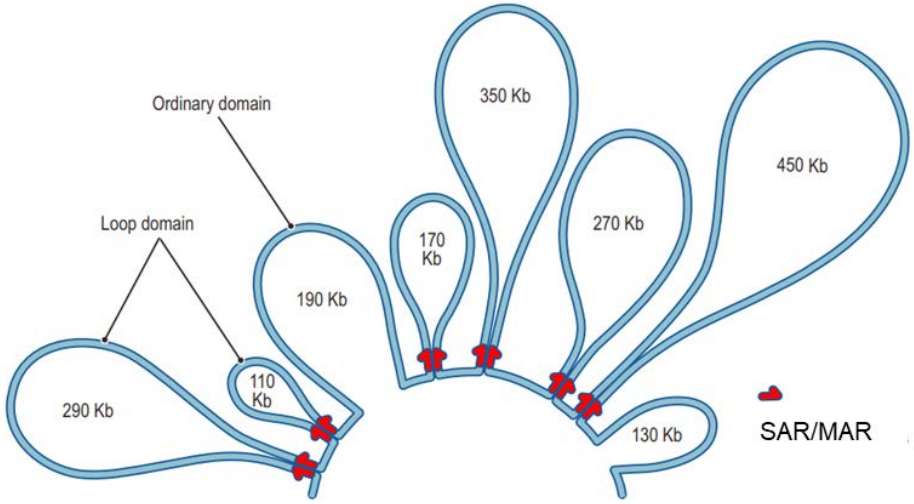
Each loop aggregates segments of DNA that are linearly distant.

Loops are anchored at specific regions called scaffold/matrix attachment regions (S/MARs).

Bring enhancers into close proximity with promoters, enabling transcriptional activation.

Help insulate or prevent enhancer-promoter interactions in neighboring loops to maintain genetic boundaries.





Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Topoisomerases and MARs

DNA is normally negatively supercoiled.

This supercoiling is essential for compacting DNA but can cause strain.

Topoisomerases resolve this by cutting and rejoining the DNA strands.

Type I Topoisomerases make a single-strand break in the DNA, allowing the DNA to unwind or relax, and then reseal the break.

Type II Topoisomerases make a double-strand break in the DNA and pass another part of the DNA molecule through the break before resealing it.

Type II topo's are essential for relieving strain caused by DNA replication and transcription.

www.youtube.com/watch?v=3QWA-tFdGN8

Domains or topologically associating domains (TADs)

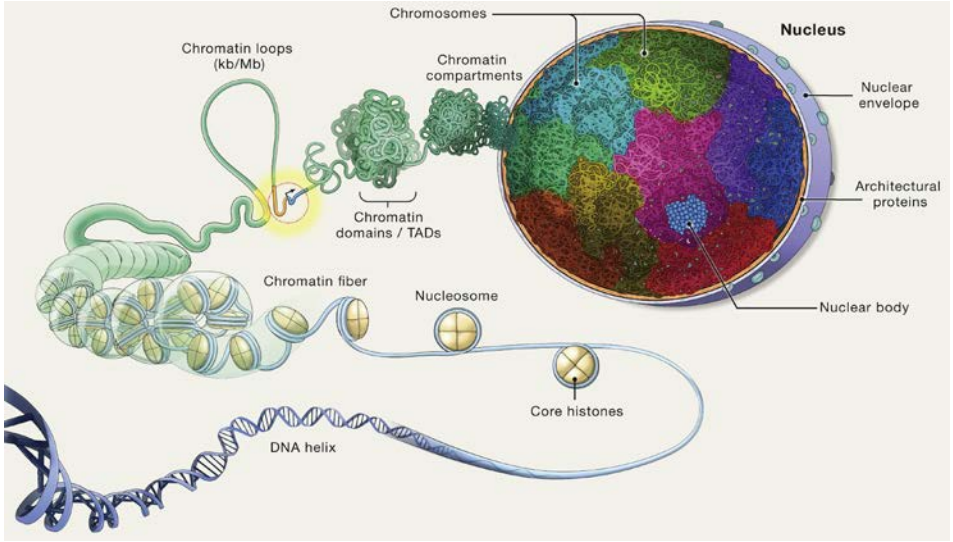
Transcriptional activity (Euchromatin) or inactivity (Heterochromatin) form homotypic domains.

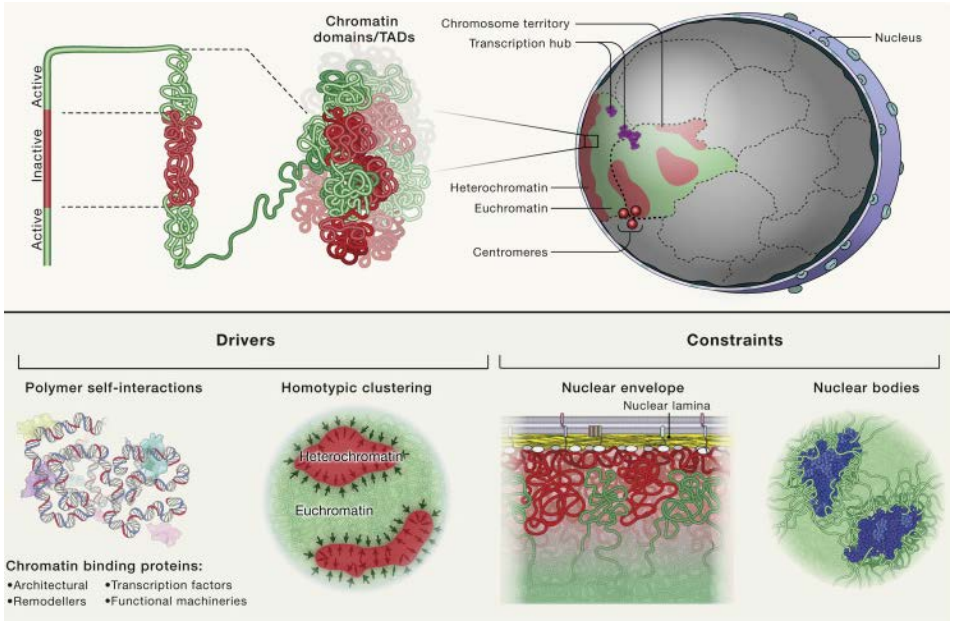
Multiple homotypic (active or inactive) domains aggregate within a chromosome or between distinct chromosomes to form compartments.

TADs are regions where sequences interact more frequently with each other.

Hundreds of kilobases to megabases.

TAD boundaries are often insulated by CTCF (a boundary-binding protein) and cohesin (a protein complex that holds loops of chromatin together).





Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Chromosome kernels and coils

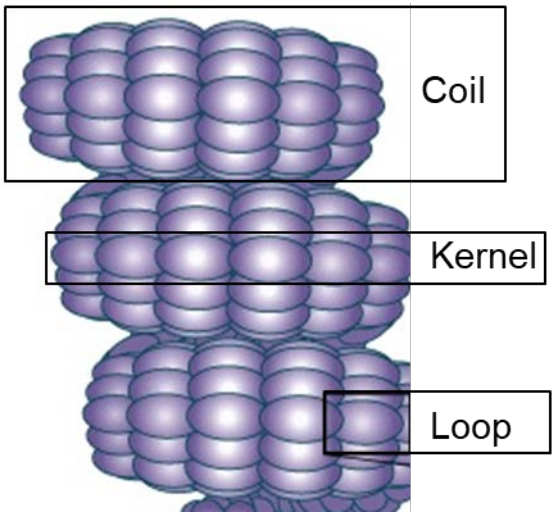
Eukaryotic chromosomes are typically linear, unlike the circular chromosomes of prokaryotes.

Centromere is a constriction point that divides the chromosome into p-arm (short arm) and q-arm (long arm).

It plays a critical role in chromosome segregation during mitosis and meiosis.

Telomeres are protective structures at the ends of chromosomes that contain repetitive sequences that prevent the loss of important genetic information during DNA replication.

Gradual telomere shortening is associated with aging and cell senescence.



Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Chromosomes

Eukaryotic chromosomes are linear, unlike the circular chromosomes of prokaryotes.

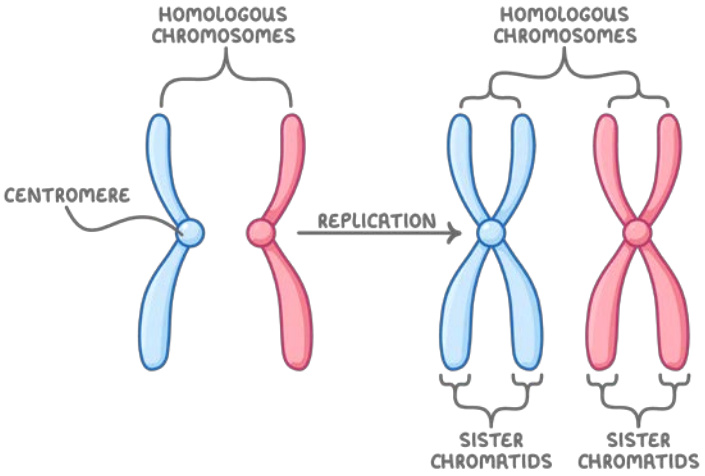
Centromere is a constriction point that divides chromosome into p-arm (short) and q-arm (long), used for segregation during mitosis and meiosis.

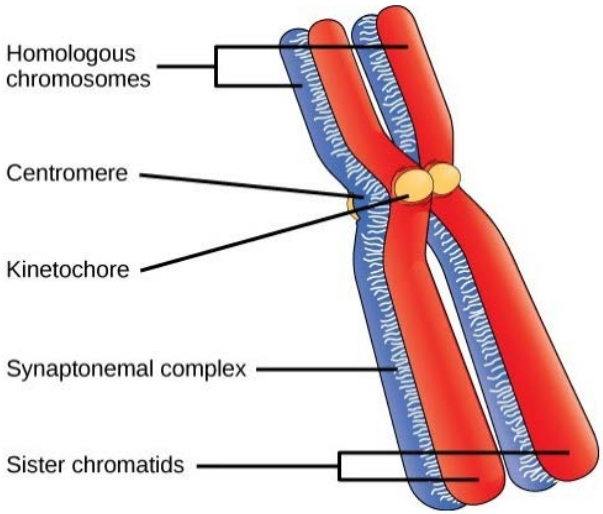
Telomeres protect ends of chromosomes and repetitive sequences prevent loss of genetic information during DNA replication.

Gradual telomere shortening is associated with aging and cell senescence.

During interphase, are decondensed and functionally active as chromatin.

During mitosis and meiosis, are condense into highly visible structures to facilitate segregation.

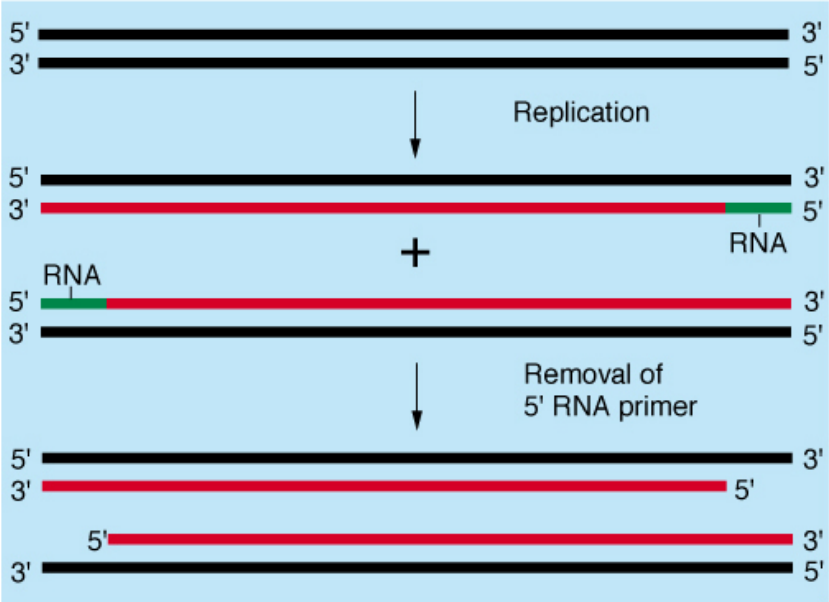




Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Telomeres and the end-replication paradigm

Paradigm addresses challenges associated with fully replicating linear genetic material where DNA polymerases cannot complete replication of the terminal ends of linear chromosomes.



Replication requires primers to initiate.

At the ends of linear DNA, once the RNA primer is removed, there is no upstream DNA for the polymerase to extend from.

The gradual shortening of telomeres in somatic cells contributes to cellular aging and may lead to genomic instability, a hallmark of cancer.

Specialized repetitive DNA sequences (e.g., TTAGGG in humans) at chromosome ends protect genes from being lost due to the end-replication problem.

Telomerase extends ends by adding repetitive sequences using an RNA template.

Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Chromosomes

The number of chromosomes varies among species.

Diploid (2n): Most eukaryotic somatic cells contain two sets of chromosomes.

Haploid (n): Gametes (sperm and egg) contain a single set of chromosomes.

Some organisms exhibit polyploidy (more than two sets of chromosomes).

Ophioglossum reticulatum, a species of adder's-tongue fern has the largest known chromosome count, with 1,440 chromosomes (720 pairs of chromosomes).

D. melanogaster	8
Guinea pig	16
Dove	16
Land snail	24
Worms	36
Fox	36
Cat	38
Pig	38
Mouse	40
Rat	42
Rabbit	44
Hamster	44
Hare	46
Human	46
Gorillas & Chimps	48
Lamb	54
Elephant	56
Cow	60
Donkey	62
Horse	64
Dog	78
Chicken	78
Goldfish	104

Cook Island 50 Tene coin ►

Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Karyotpe

Errors in chromosome number or structure can lead to genetic disorders:

Aneuploidy: Extra or missing chromosomes (e.g., Down syndrome, Turner syndrome).

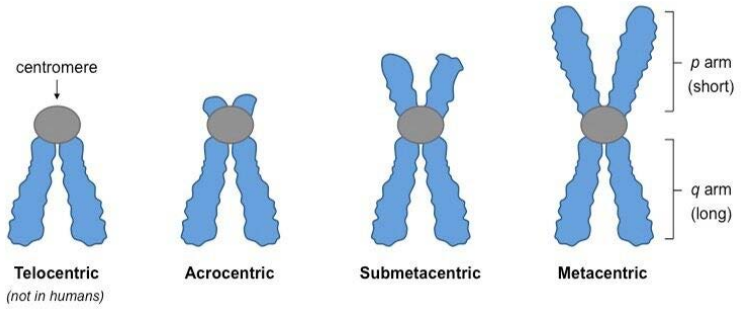
Structural Variations: Deletions, duplications, translocations, or inversions.

Chromosome 1, largest with ~249 Mbp.

Chromosome 21, smallest with ~48 Mbp.

The X chromosome has ~1,000 genes, while the Y chromosome has only about 55 protein-coding genes.

A karyotype is the complete set of chromosomes in an organism, arranged and visualized in a standard format, typically in terms of their number, size, shape, and banding patterns.

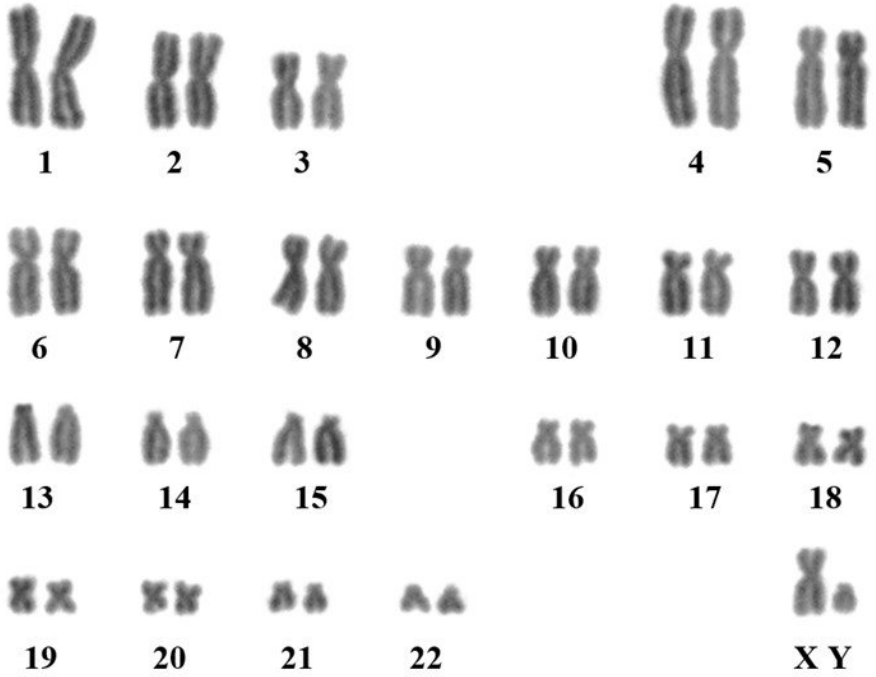


Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Karyotpe

A karyotpe provides a snapshot of the chromosomal composition of an organism's cells and is a crucial tool in genetics for identifying abnormalities, studying evolution, and conducting species-specific research.

Normal karyotype technique

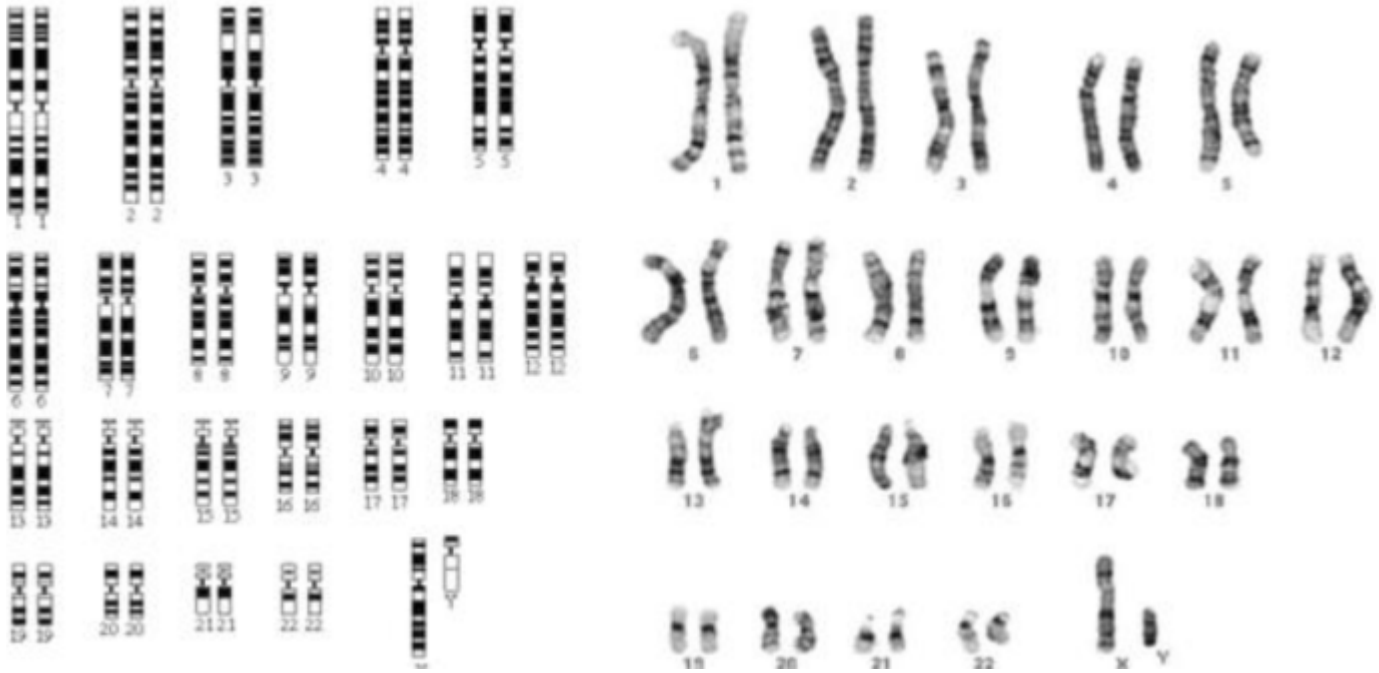


Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Karyotpe

A karyotpe provides a snapshot of the chromosomal composition of an organism's cells and is a crucial tool in genetics for identifying abnormalities, studying evolution, and conducting species-specific research.

G-band karyotype technique

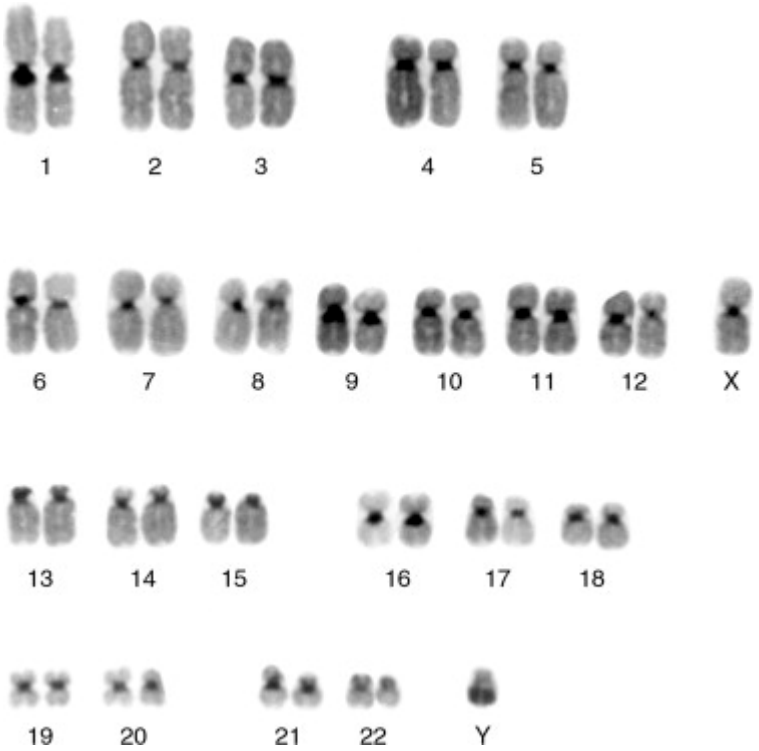


Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Karyotpe

A karyotpe provides a snapshot of the chromosomal composition of an organism's cells and is a crucial tool in genetics for identifying abnormalities, studying evolution, and conducting species-specific research.

C-band karyotype technique



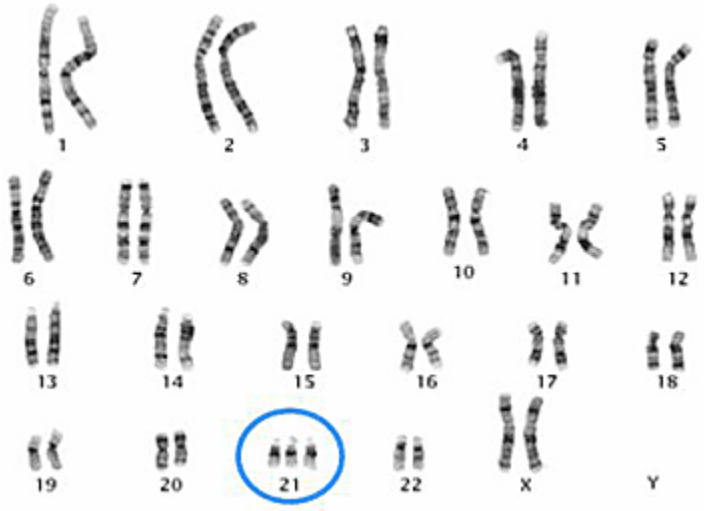
Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

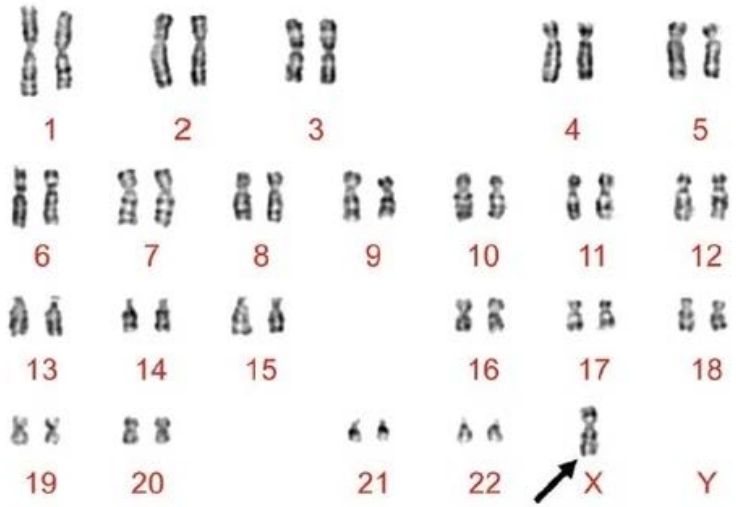
Chromosome number anomalies

A condition where the number of chromosomes is not the typical number for the species, either due to the presence of an extra chromosome or the absence of one.

Trisomy
The presence of an extra chromosome (e.g., Down syndrome with Trisomy 21).

Monosomy
The absence of one chromosome from a pair (e.g., Turner syndrome with Mono X).





Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Chromosome number anomalies

Down Syndrome: 47, XY, +21 or 47, XX, +21

Turner Syndrome: 45, X

Klinefelter Syndrome: 47, XXY

Triple X Syndrome: 47, XXX

Jacobs Syndrome: 47, XYY

Cri du Chat Syndrome: 46, XX, 5p−

Prader-Willi Syndrome: 46, XX, 15q11-q13 deletion

Angelman Syndrome: 46, XX, 15q11-q13 deletion

Williams Syndrome: 46, XX, 7q11.23 deletion

DiGeorge Syndrome: 46, XX, 22q11.2 deletion

Ring Chromosome 14 Syndrome: 46, XX, r(14)

Wolf-Hirschhorn Syndrome: 46, XX, 4p−

Chronic Myelogenous Leukemia (CML): 46, XY, t(9;22)(q34;q11)

Patau Syndrome (Trisomy 13): 47, XY, +13 or 47, XX, +13

Chromosome structure anomalies

These types of abnormalities affect the structure of the chromosomes rather than the number of chromosomes.

Translocation:
A segment of one chromosome is transferred to another chromosome.

Inversion:
A section of a chromosome is reversed 180 degrees.

Deletion:
A portion of a chromosome is lost.

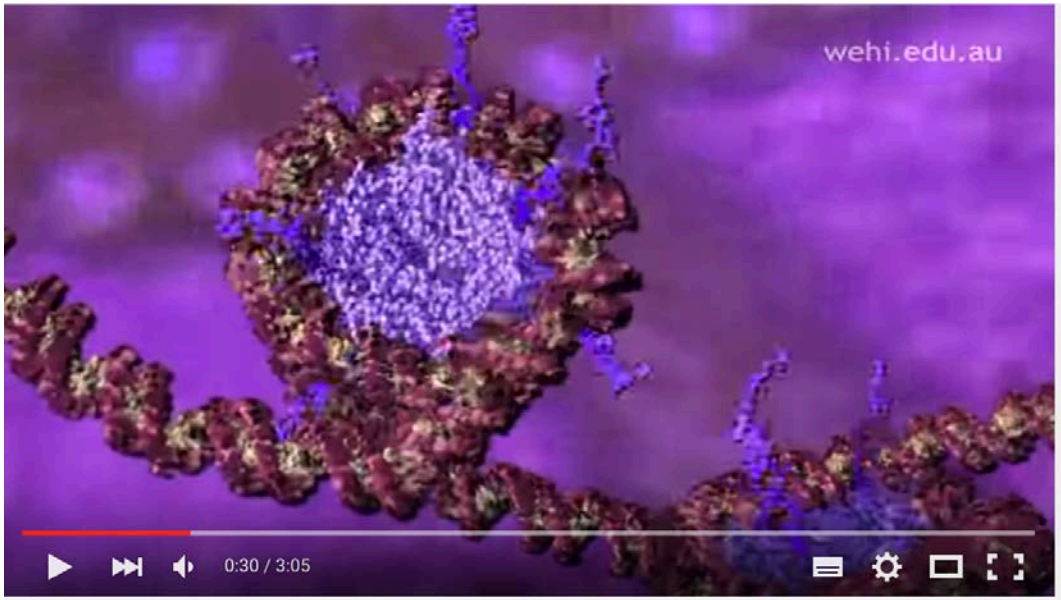
Duplication:
A section of a chromosome is repeated, leading to multiple copies of a particular region.

Ring Chromosome:
A chromosome that forms a ring shape due to deletions at both ends and fusion of the chromosome ends.

Isochromosome:
A chromosome with identical arms due to the loss of one arm and duplication of the other.

Misteli, Tom, The Self-Organizing Genome: Principles of Genome Architecture and Function Cell, Volume 183, Issue 1, 28 - 45

Compactación y jerarquias organizacionales

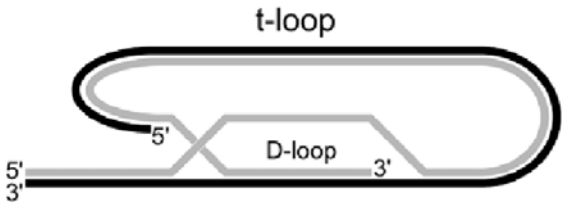


Molecular Visualizations of DNA - Original High Quality Version

https://www.youtube.com/watch?v=OjPcT1uUZiE

Telomeres

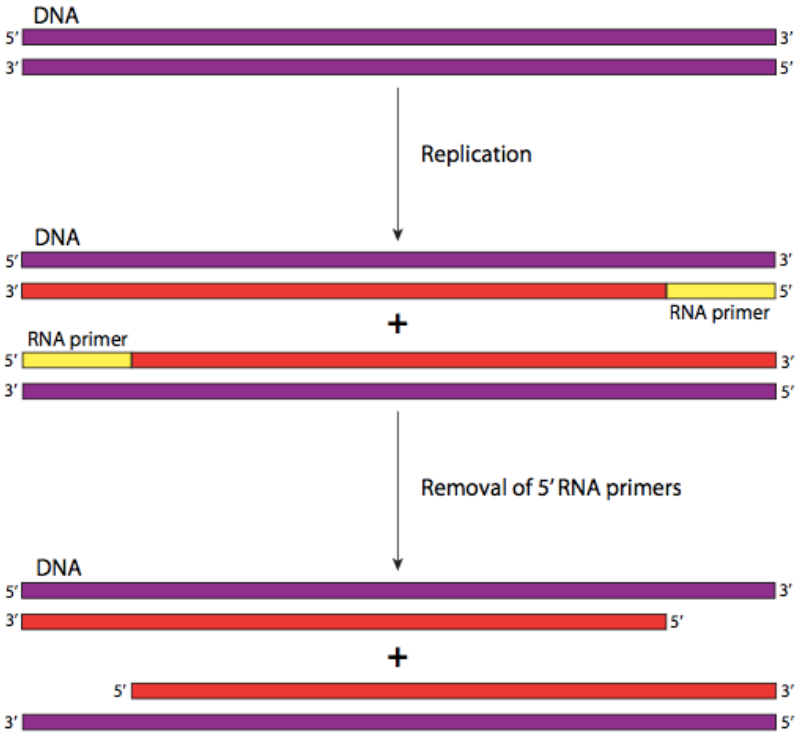
Telomeres are repetitive nucleotide sequences located at the ends of linear eukaryotic chromosomes.



They serve several critical functions:

Protection of Chromosome Ends
Telomeres prevent chromosome ends from being recognized as DNA damage, which would trigger repair mechanisms or cell cycle arrest.

Terminal Replication Paradigm Solution
During DNA replication, the lagging strand cannot be fully replicated at the ends, leading to the loss of some sequence with each division. Telomeres act as buffers to protect coding regions of the genome from this loss.



Telomeres

Sequence Composition

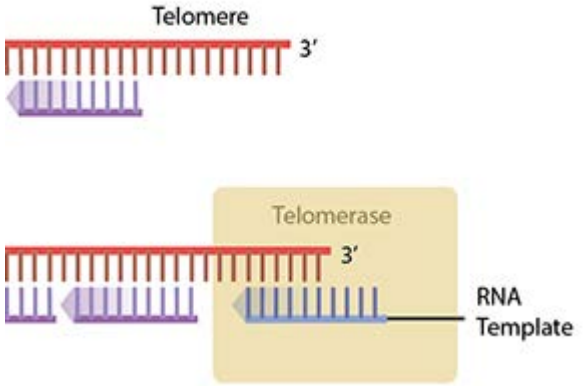
Telomeres are typically composed of short, tandemly repeated sequences, such as TTAGGG in humans and other vertebrates.

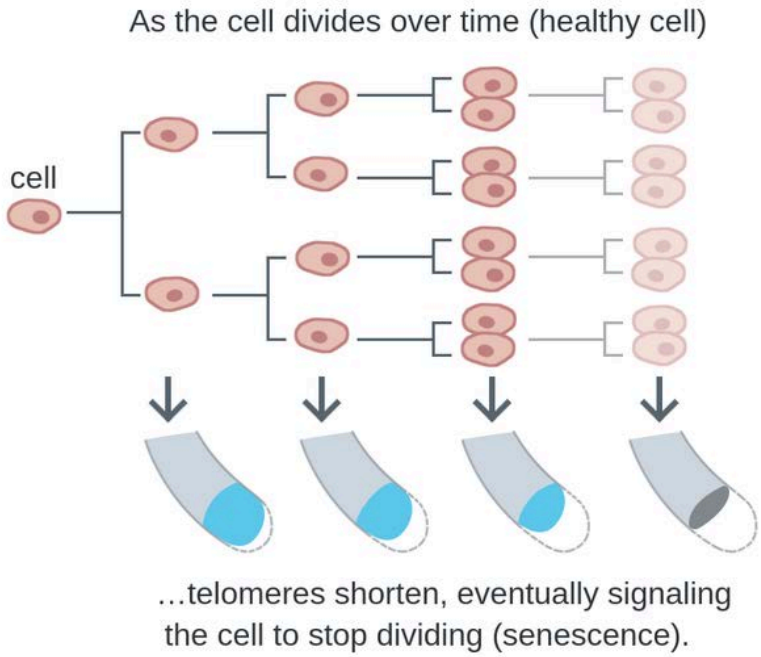
Association with Telomerase

The enzyme telomerase extends telomeres by adding repeats to the ends, counteracting the natural shortening that occurs during DNA replication.

Aging and Senescence

Telomeres shorten with each cell division in most somatic cells due to the absence or low activity of telomerase, eventually leading to replicative senescence or cellular aging.





Telomeres

Cancer Connection

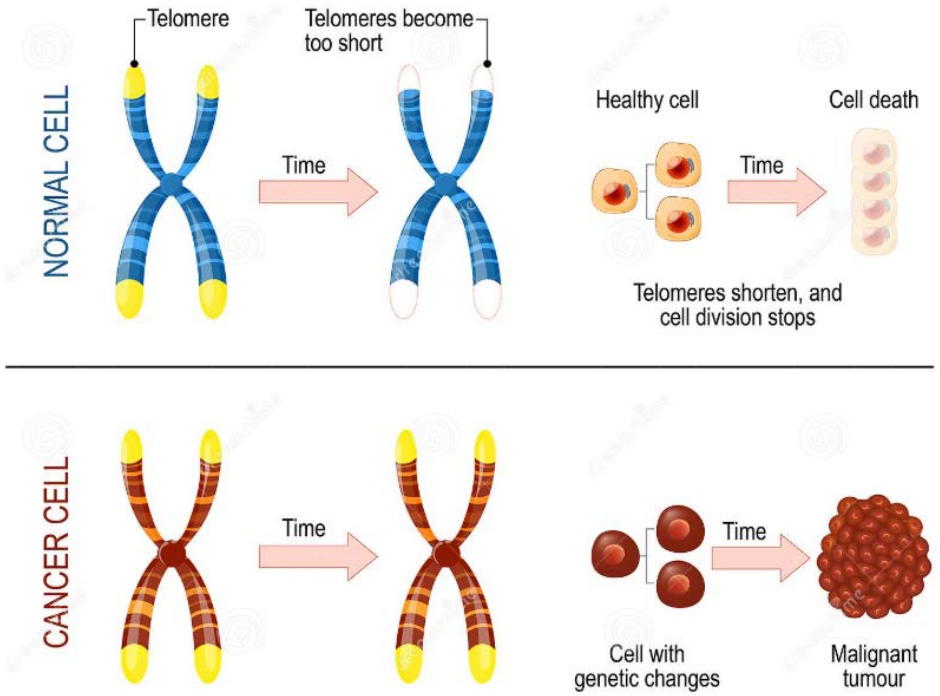
Many cancer cells reactivate telomerase to maintain telomere length, enabling unlimited cell divisions and contributing to their immortality.

Shelterin Complex

Telomeres are bound by a protein complex called shelterin, which protects the telomeres from degradation and regulates telomere length.

Role in Chromosomal Stability

Telomeres prevent chromosomal ends from fusing with each other, maintaining genomic integrity.



Telomerase

Telomerase is a ribonucleoprotein enzyme that maintains telomere length, essential for chromosome end protection.

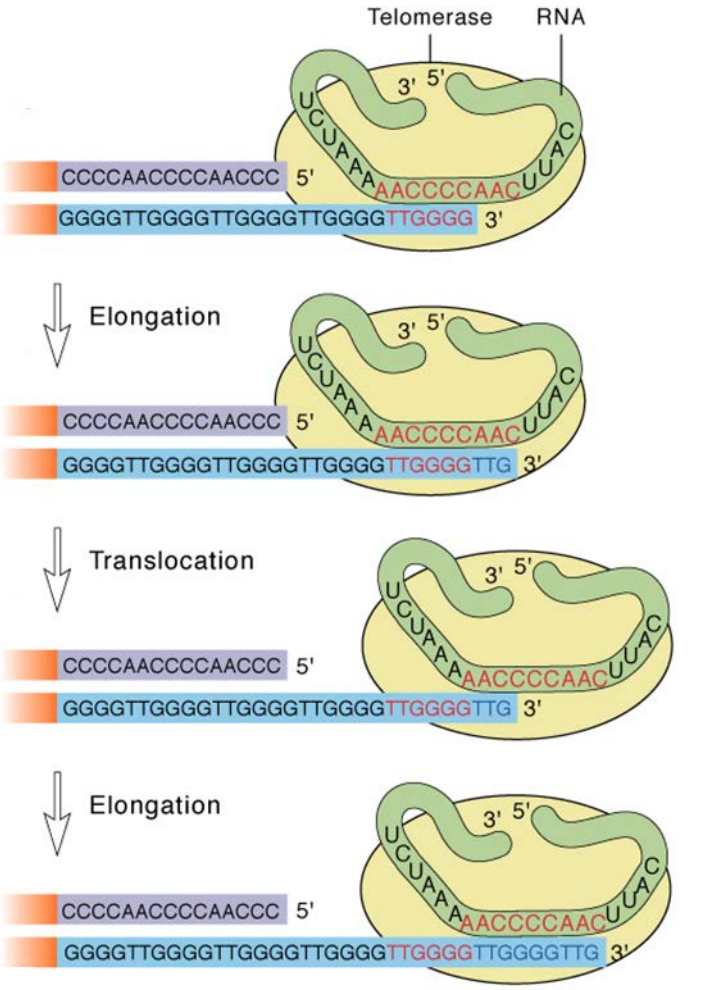
TERT: Catalytic protein subunit (Telomerase Reverse Transcriptase).

TERC: RNA molecule serving as the template for telomere extension.

Extends the 3' overhang of telomeres, counteracting shortening during DNA replication.

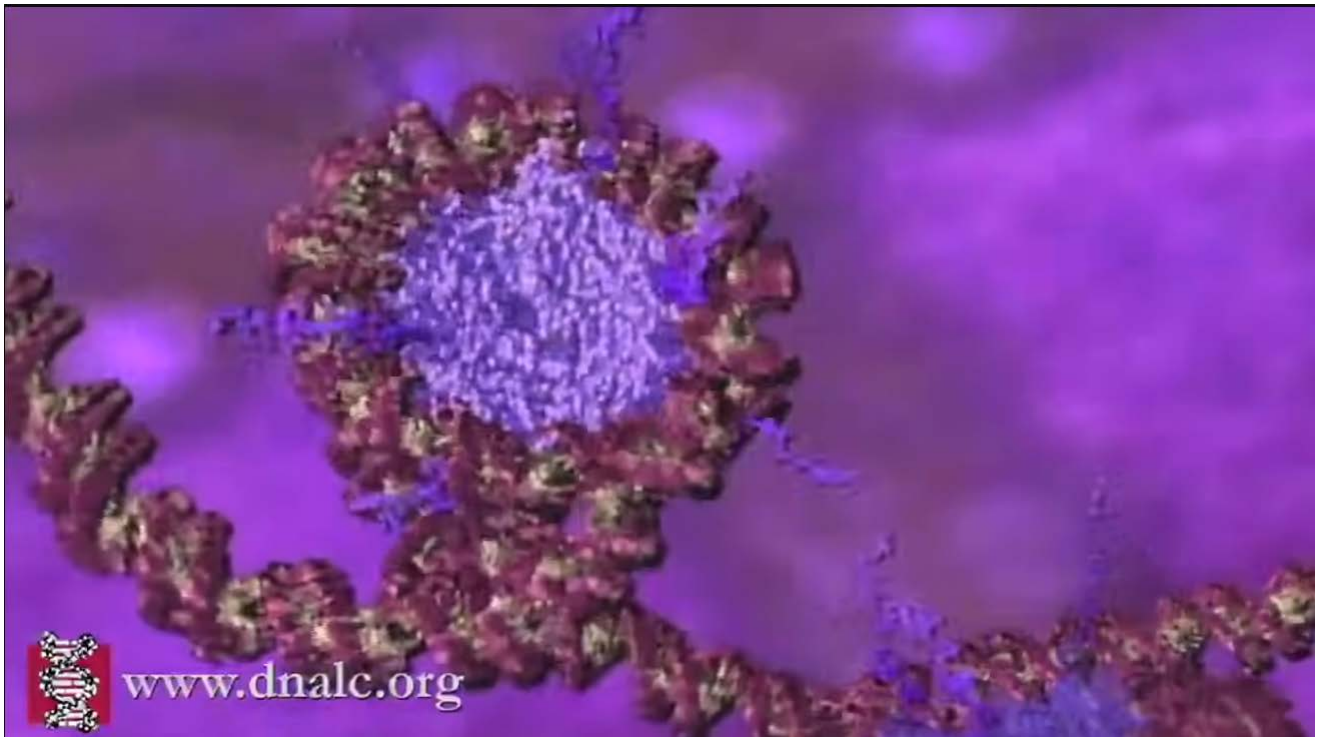
Active in germ cells, stem cells, and certain immune cells.

Inactive or low in most somatic cells, leading to telomere shortening and aging.



Reactivated in cancer cells, enabling indefinite proliferation bypassing senescence.

Overview of eukaryotic compaction



www.youtube.com/watch?v=gbSIBhFwQ4s

Viral & Human Genomics Laboratory

CDC Commissioned Biosafety Level 3 (BSL-3) High Biocontainment Facility

Laboratorio de Genómica Viral y Humana

Instalaciones de Alta Contención Biológica Nivel de Bioseguridad 3 (BSL-3) CDC-certificadas

Facultad de Medicina UASLP
San Luis Potosí, México

www.genomica.uaslp.mx

GenomicaUASLP

YouTube GenomicaUASLP