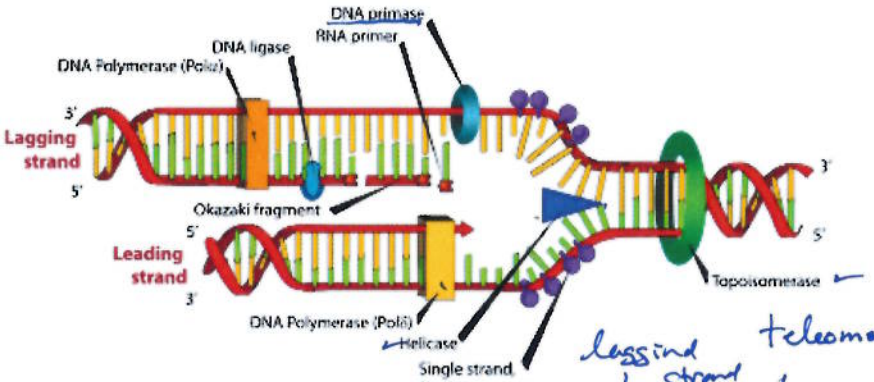
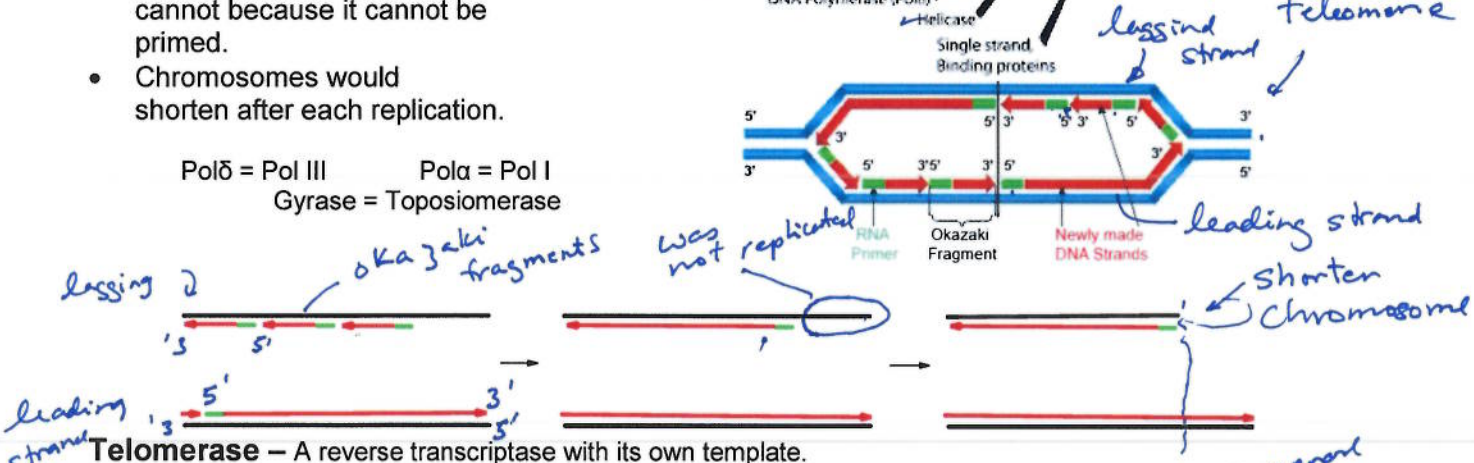
Lecture 32: Replication of Chromosomes, Histone modification, Mitosis.



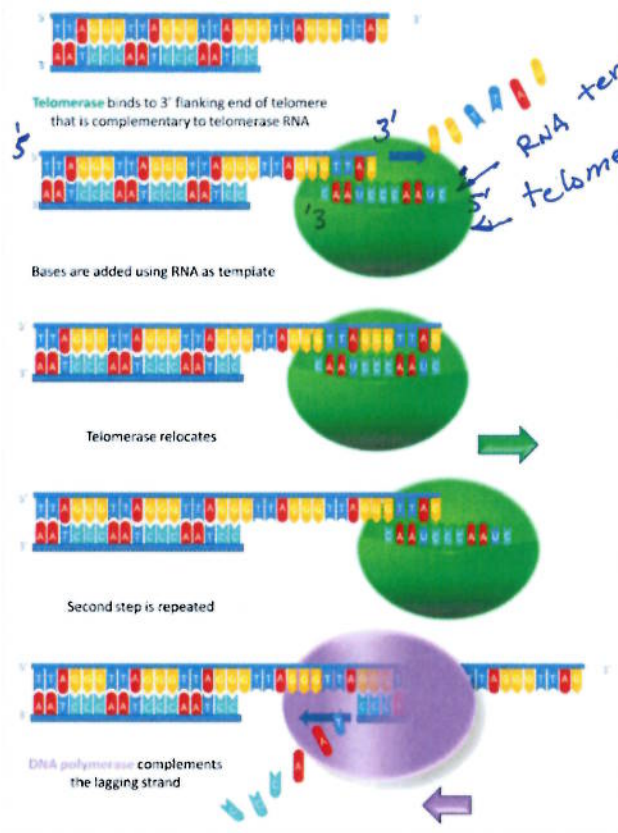
What to do at the ends?

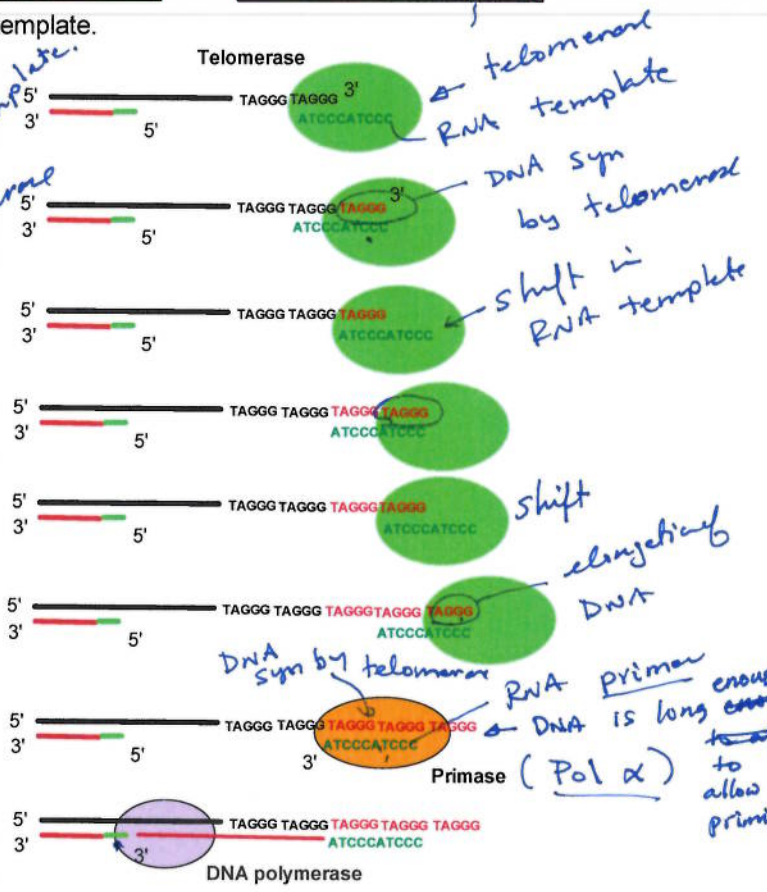
- The lower strand can be replicated to its end as part of the leading strand synthesis.
- The upper, lagging, strand cannot because it cannot be primed.
- Chromosomes would shorten after each replication.

Polδ = Pol III Polα = Pol I
Gyrase = Toposiomerase



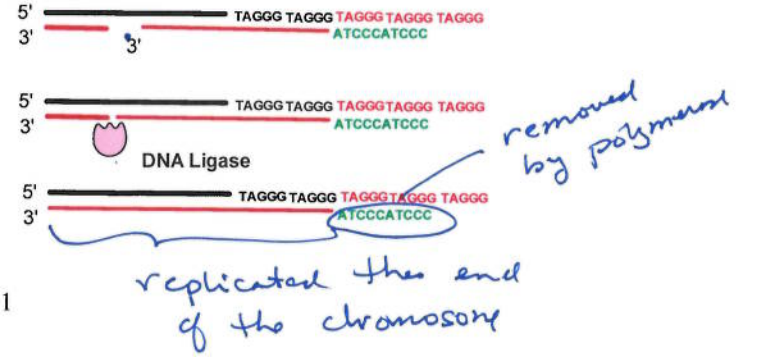
Telomerase – A reverse transcriptase with its own template.





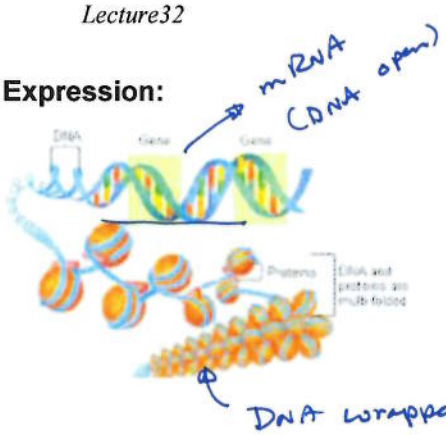
Telomerase and Cancer:

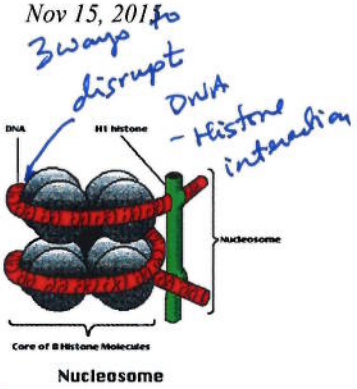
- normal cells produce low levels of telomerase and have a limited number of cell divisions.
- Cancer cells often have elevated levels of telomerase, allowing them to divide an infinite number of times.



Histone Modification and Regulation of Gene Expression:

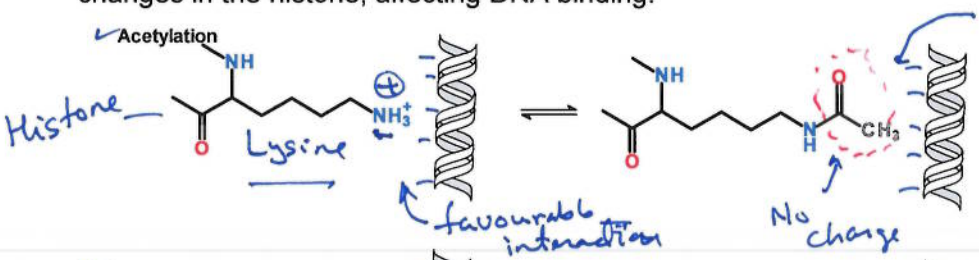
- DNA that is highly condensed is not available for transcription.
- Modification of histones can restructure the chromosome, allowing or inhibiting transcription.
- Common modification of histones include:
  - Acetylation of lysine residues
  - Phosphorylation of Serine and Tyrosine residues
  - Methylation of lysine residues.

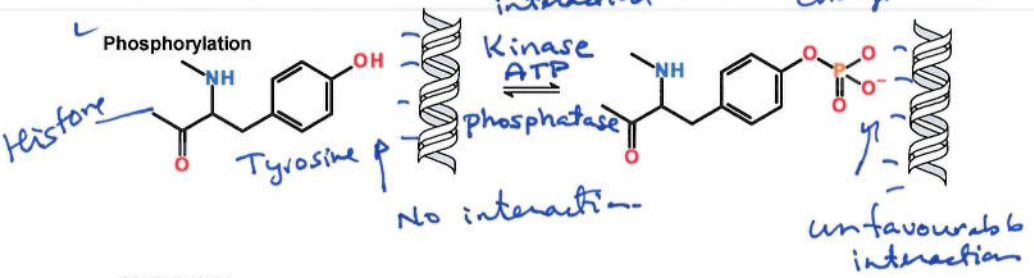


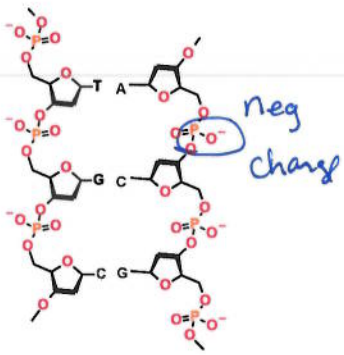


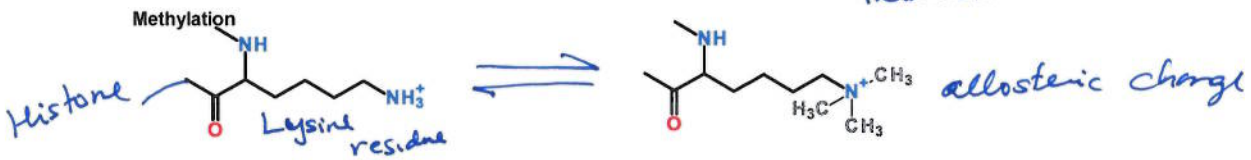
Nucleosome

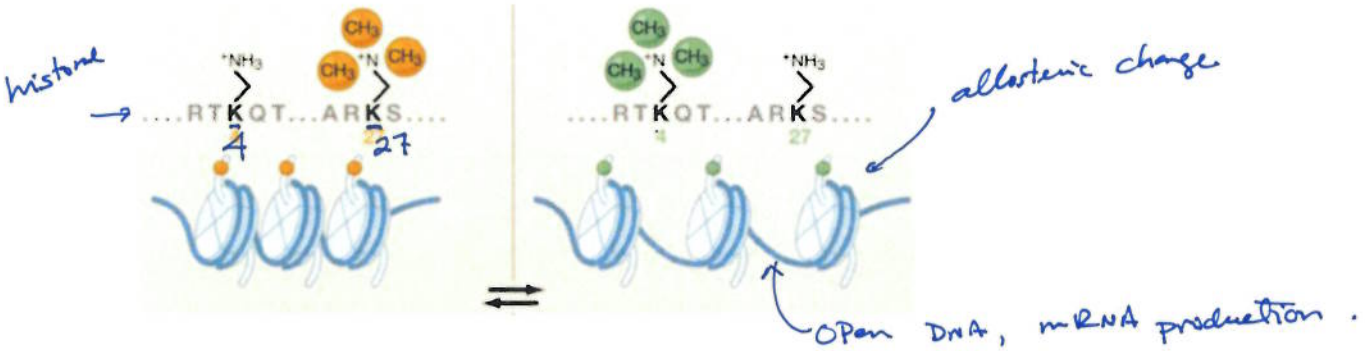
The site of and type of modification can affect whether the DNA is accessible for transcription. For example, methylation of lysine at position 4 or 27 in a histone causes different conformational changes in the histone, affecting DNA binding.











Comparison of Regulation and Diversity of Eukaryotic and Prokaryotic Proteins:

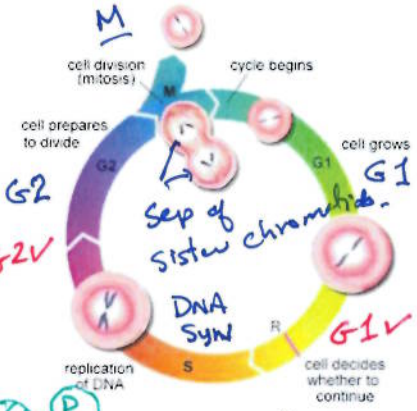
Prokaryotic Cells	Eukaryotic Cells
Transcriptional Control	
Repressors	Repressors
Activators	Activators (enhancers/transcription factors)
	DNA accessibility (histone modification)
mRNA Stability and Processing	
	mRNA stability (poly A)
	Alternative spicing

Replication of Body (somatic) cells (Chapter 13):

- Maintain diploid number of chromosomes 2n → 2n
- Exact copy of Genetic material in daughter cells.

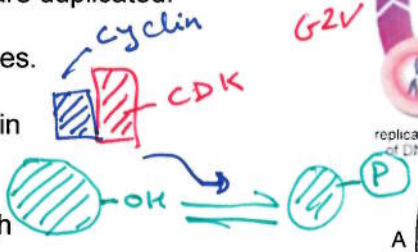
Cell cycle:

G1 – cell growth
S – replication of DNA, chromosomes are duplicated.
G2 – Prior to division
M – **mitosis**, separation of chromosomes.

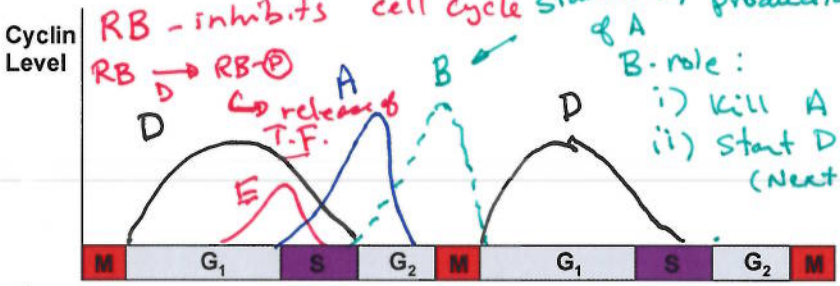


Interphase = G1-S-G2

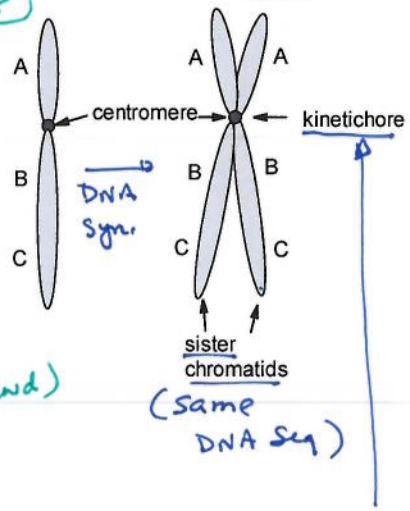
- Cell cycle regulated by cyclins and cyclin dependent protein kinases (CDK).
- The cyclin-CDK complex act to kinase proteins involved in progression through cell cycle.
- Order of expression of cyclins is:
  D (G1) → E (G1/S) → A (S/G2) → B (M)



The appearance of the next cyclin leads to the destruction of the previous:



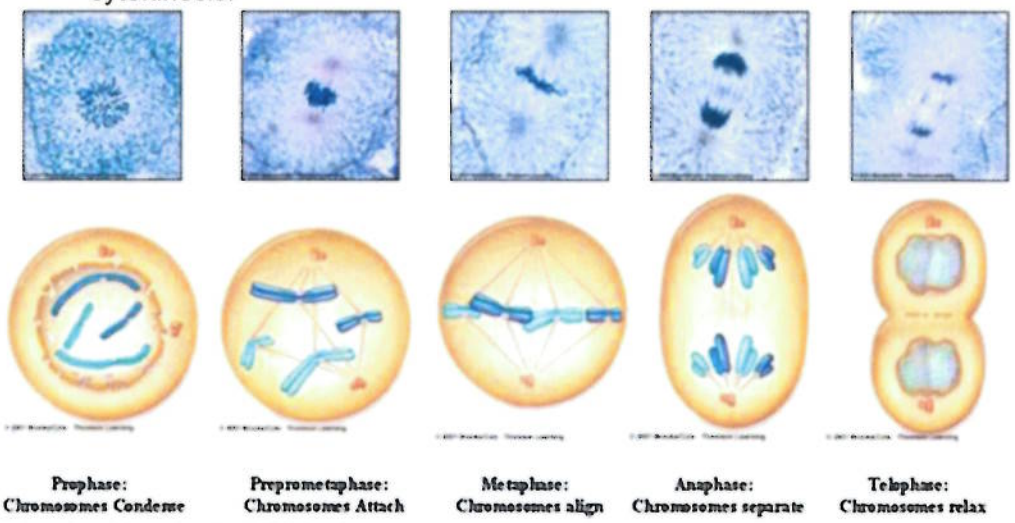
B-role:
i) kill A
ii) start D (Next round)



Mitosis:

1. Prophase – chromosomes condense, spindle forms. Spindle is organized by **centrosomes**.
2. Prometaphase: Nuclear membrane disappears. Spindle fibers (**microtubules**) attach to **kinetichore** on duplicated chromosomes
3. Metaphase: Chromosomes align at the center of the cell
4. Anaphase: Sister chromatids separate, pulled to opposite poles of cell by microtubules.
5. Telophase: Nuclear membrane reappears, spindle disappears. Daughter cells formed by cytokinesis.

Spindle fibers attach



Checkpoints in Cell Division:

G1 checkpoint (R) – DNA must be intact for replication
G2 checkpoint: - DNA must be fully replicated and not damaged.

Cancer and Cell Division:

p53 – detects DNA damage and arrests cell division. G2

RB (retinoblastoma) – suppresses activity of E2F transcription factor, until cyclin D is activated. Mutations in RB lead to tumors in the eye (retinoblastomas) because E2F is always active, leading to uncontrolled cell division by the activation of genes required for cell cycle.