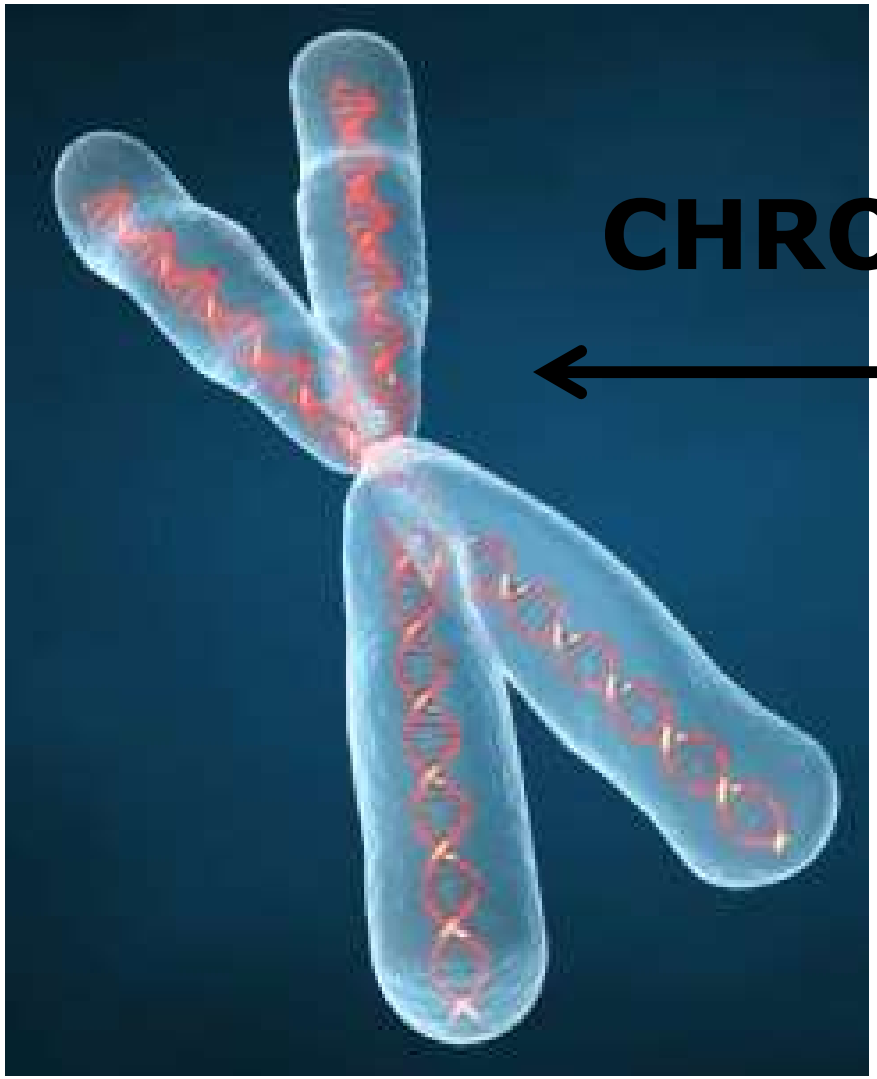
THE CELL CYCLE

MAKING BRAND NEW CELLS!

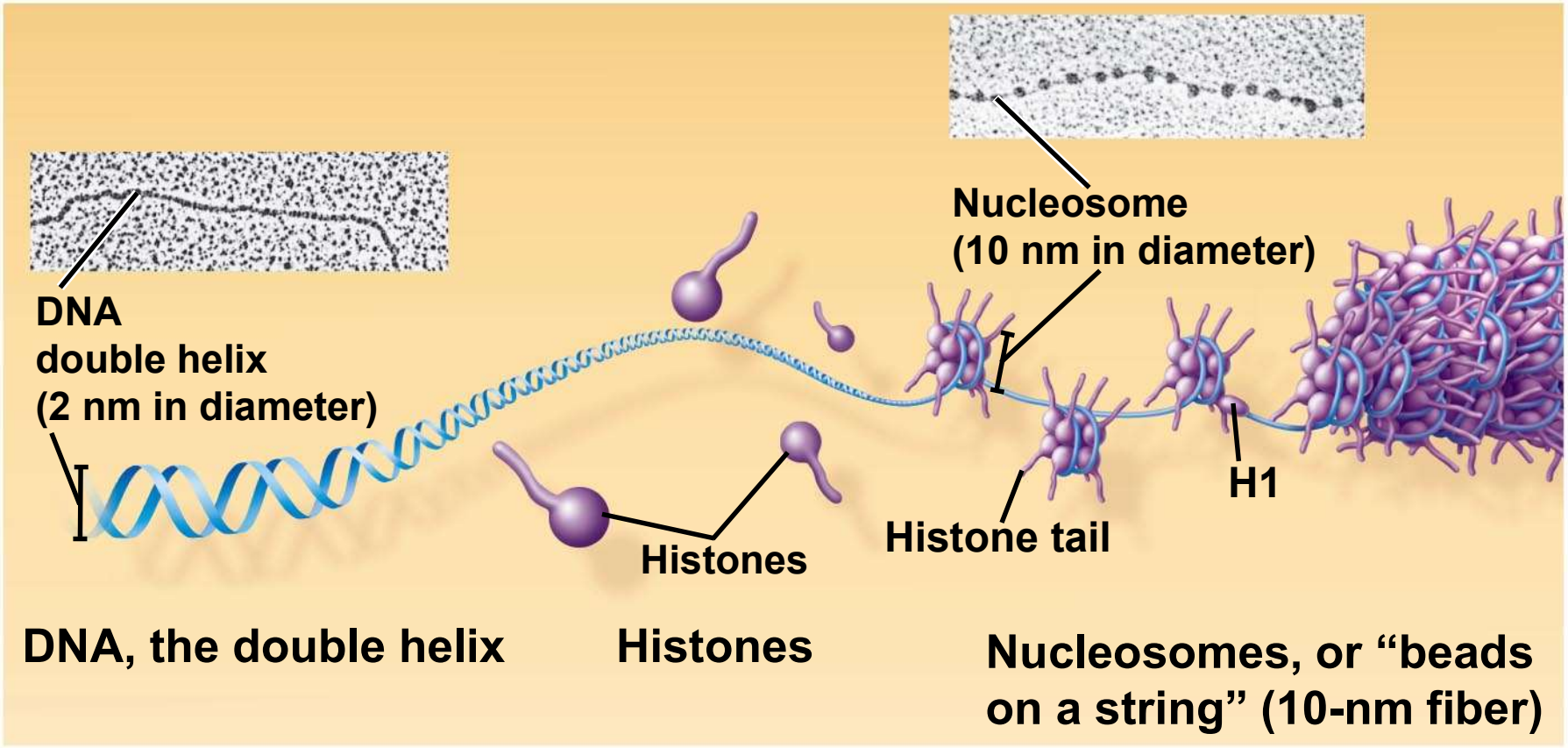
LABEL THE IMAGES AS WE GO



CHROMOSOME

Review of Chromatin Structure

- **Chromatin** is a complex of DNA and protein in the eukaryotic nucleus
- Loosely packed chromatin is called **euchromatin**
- Dense packing of the **heterochromatin** makes it difficult for the cell to express genetic information coded in these regions
- **Histones** are proteins that are responsible for the first level of DNA packing in chromatin



Every hour, about one billion (10^9) cells die and one billion cells are made in your body. Part of the cell cycle includes making new cells in a process called **cell division**.

What is the Cell Cycle?

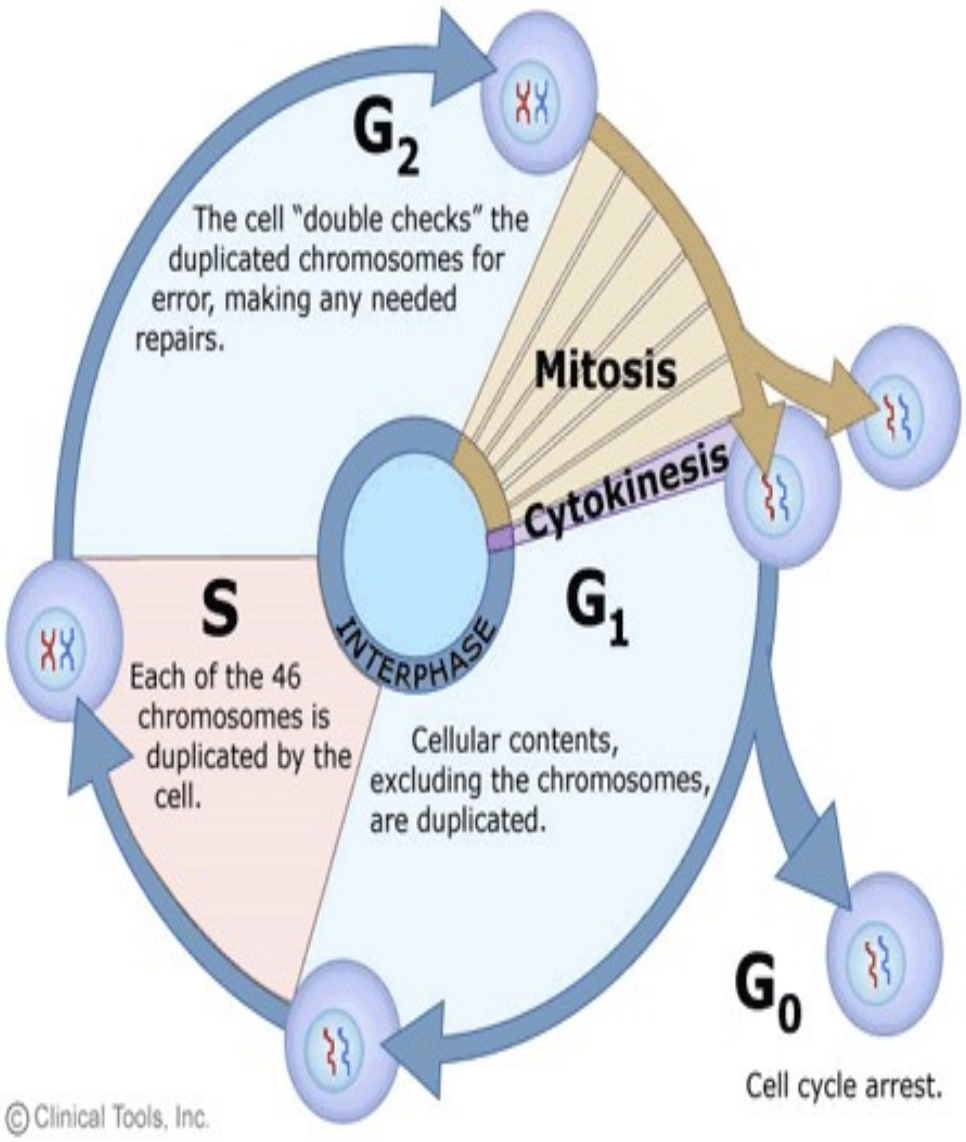
- It is the life of a eukaryotic cell: The way the cells grow, make new copies and divide!
- It happens in all of your somatic(body) cells in order to get the same DNA inside each cell. (your reproductive cells do something different)

- **The <u>largest</u> phase in which 95% of growth occurs**

- **The cell is <u>growing</u>, copying it's DNA and preparing for division**

- **<u>3 phases</u> of interphase:**

G1, S & G2



quiescent or arrested phase known as G0

1. G1

Growth of the cell in size and development (differentiation- the cell is told what to become).

2. S

Synthesis of DNA, also called REPLICATION:

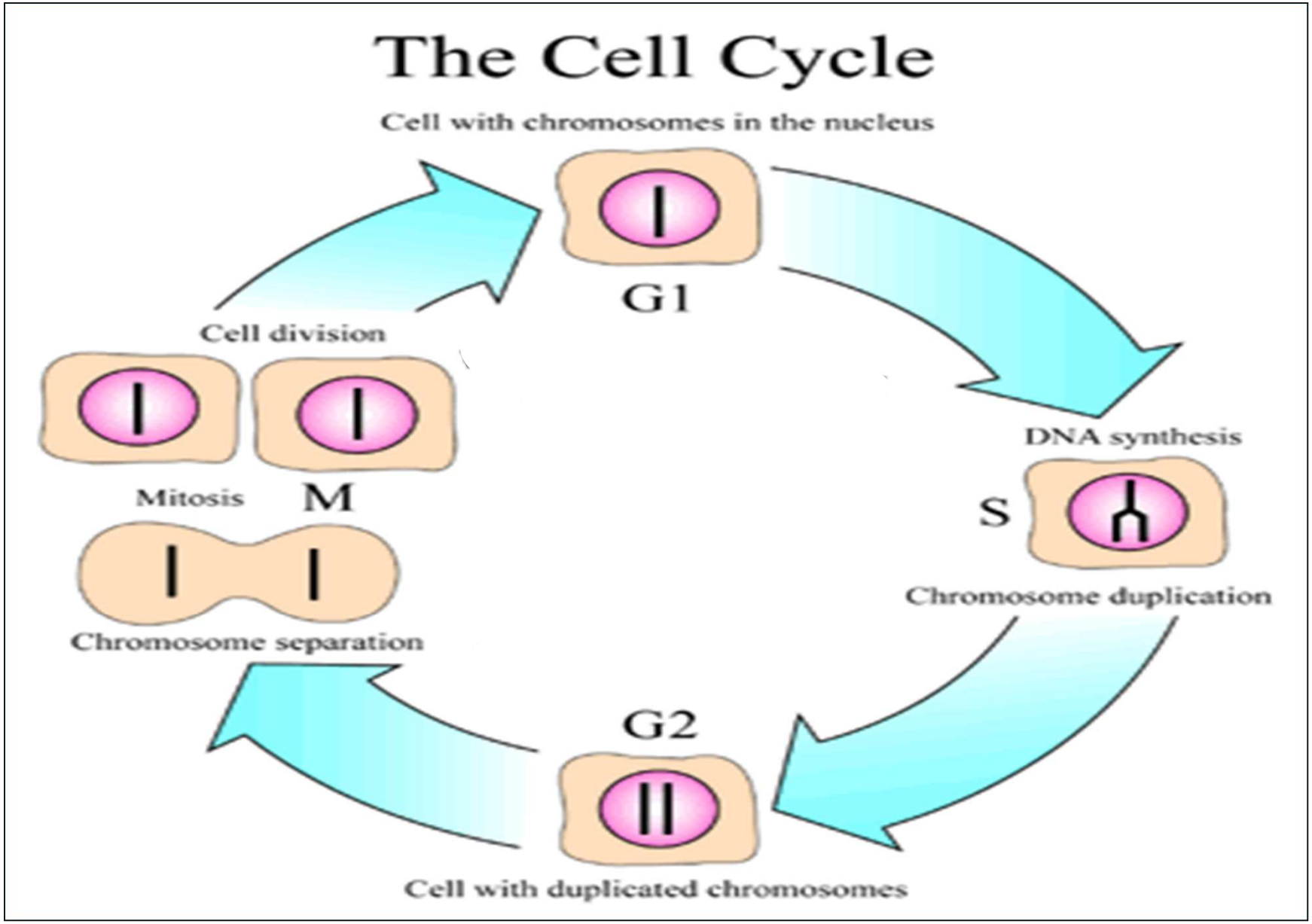
1. The DNA double helix is unzipped completely by an enzyme called HELICASE.

2. One DNA nucleotide at a time is added to BOTH sides of the DNA strand (A→T and C→G) with the help of another enzyme called DNA POLYMERASE.

3. The nucleus is left with TWO exact copies of ALL the chromosomes/DNA.

3. G2

the cell prepares for division and checks for errors.


The Cell Cycle
Cell with chromosomes in the nucleus
G1
DNA synthesis
S
Chromosome duplication
G2
Cell with duplicated chromosomes
Mitosis
M
Chromosome separation
Cell division

MITOSIS is after Interphase…

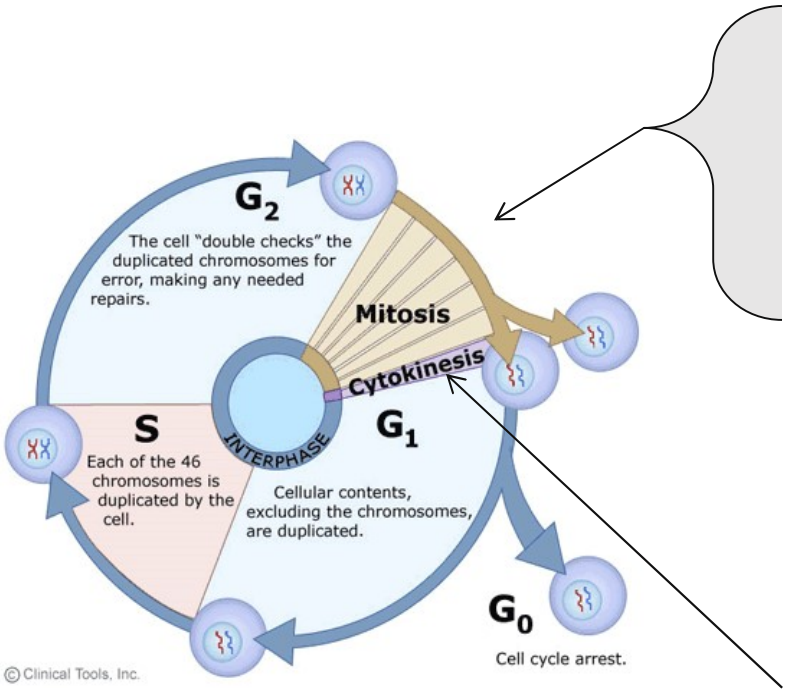
Four Phases are a part of Mitosis:

Prophase

Metaphase

Anaphase

Telophase



Cytokinesis is after mitosis

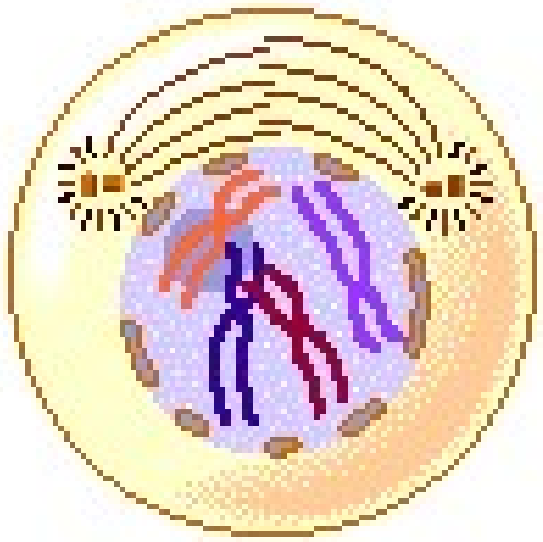
PROPHASE

- **the first phase in mitosis**
- **THREE THINGS TO LOOK FOR:**

1.chromosomes can be seen as two chromatids, in the shape of an "X"

2.Nuclear envelope dissolves

3.Centrioles are present with some spindle fibers



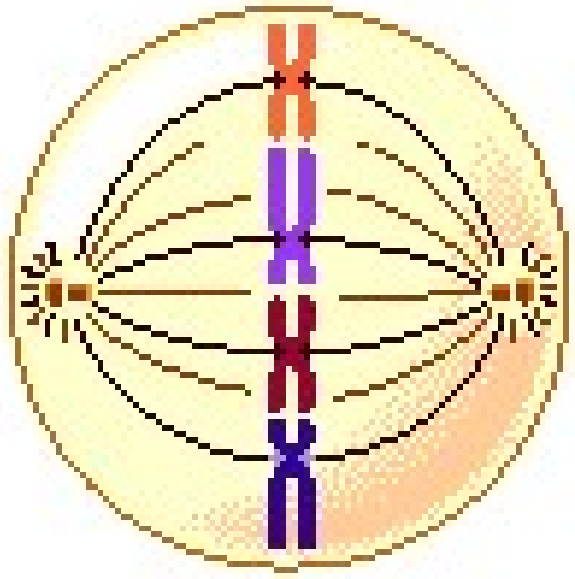
METAPHASE

- **Second phase in Mitosis**
- **THREE THINGS TO LOOK FOR:**

1.chromosomes line up in the middle

2.Nuclear envelope is gone (no nucleus)

3.Spindle fibers (on opposite poles) are stretching towards the chromosomes



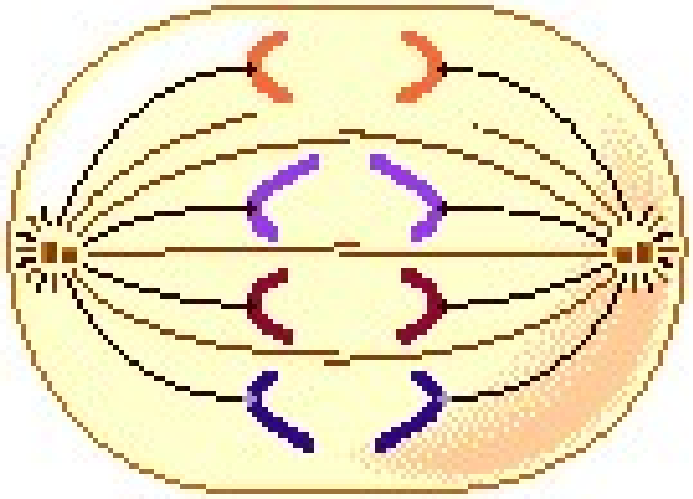
ANAPHASE

- **Third phase of Mitosis**
- **THREE THINGS TO LOOK FOR:**

1.Spindle fibers pull chromosomes towards the separate poles

2.Chromosomes are split in HALF

3.Sister chromatids are now their OWN chromosome.



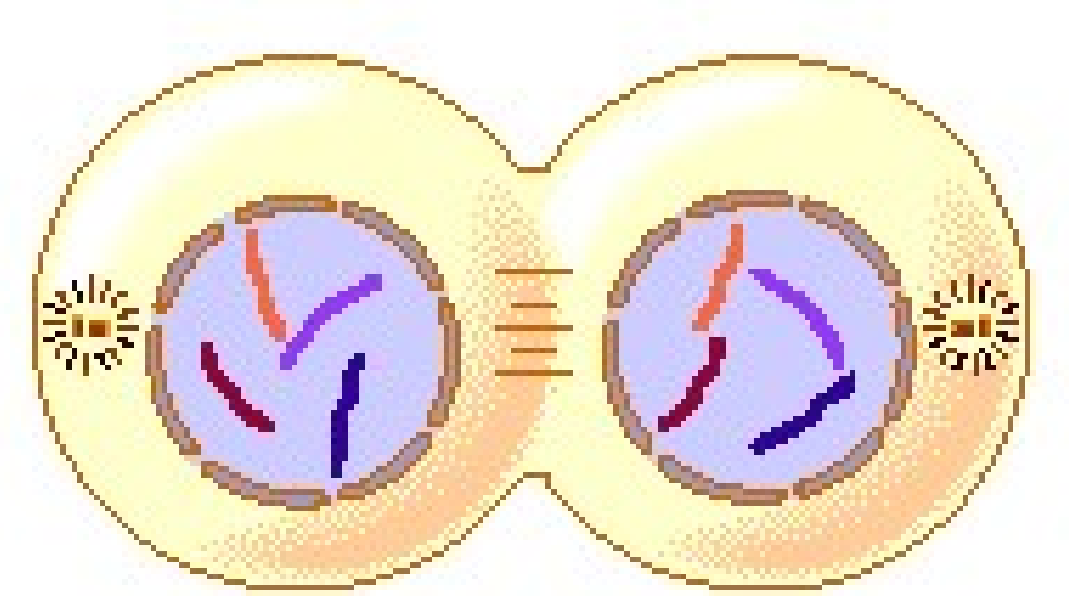
TELOPHASE

- **the final stage of Mitosis**
- **THREE THINGS TO LOOK FOR:**

1. The nuclear envelope reforms around each set of chromosomes (so daughter cells each have one) and chromosomes straighten out (uncoil)

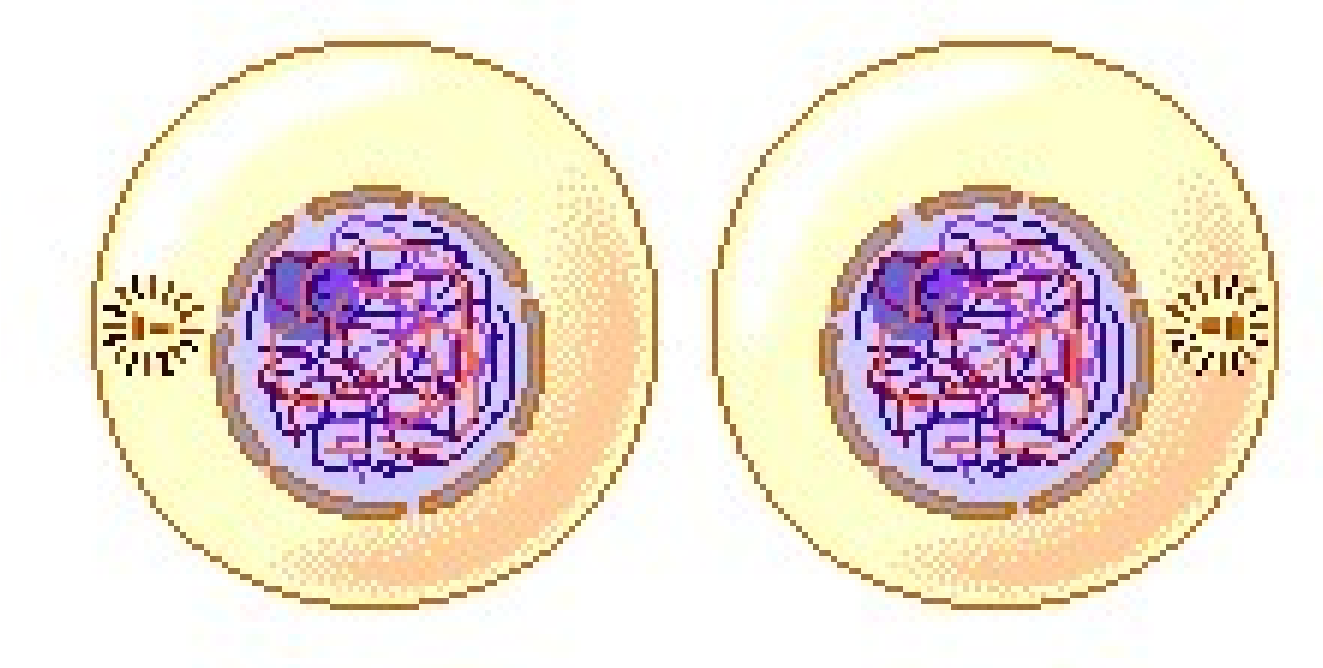
2. Spindle fibers are gone

3. Cleavage furrow is forming between the cells



CYTOKINESIS

- **Interphase → Mitosis → Cytokinesis**
- **Final step in the Cell Cycle**
- **Actually means "cell moving"**
- **The final pinching of the cell into two complete identical cells!**



Certain genes and enzymes trigger the start of the cell cycle (replication) and also tell the cells what to do.

Importance of the cell cycle to the growth of organisms:

- UNICELLULAR:

Cell cycle is how they reproduce offspring

- MULTICELLULAR:

Cell cycle is how they become an adult from only one fertilized zygote cell.

Cell Cycle in Multicellular Organisms:

- GROWTH: increase in number of cells and the size of cells (interphase G1)
- DIFFERENTIATION: cells are told by a gene to become specialized (ex. Muscle cells are told to do that job)
- MORPHOGENESIS: the patterned formation of specialized cells to become TISSUES!

Disruptions in the cell cycle:

- If certain enzymes and genes tell the cell cycle to begin too rapidly, cell division becomes out of control.

=CANCER!

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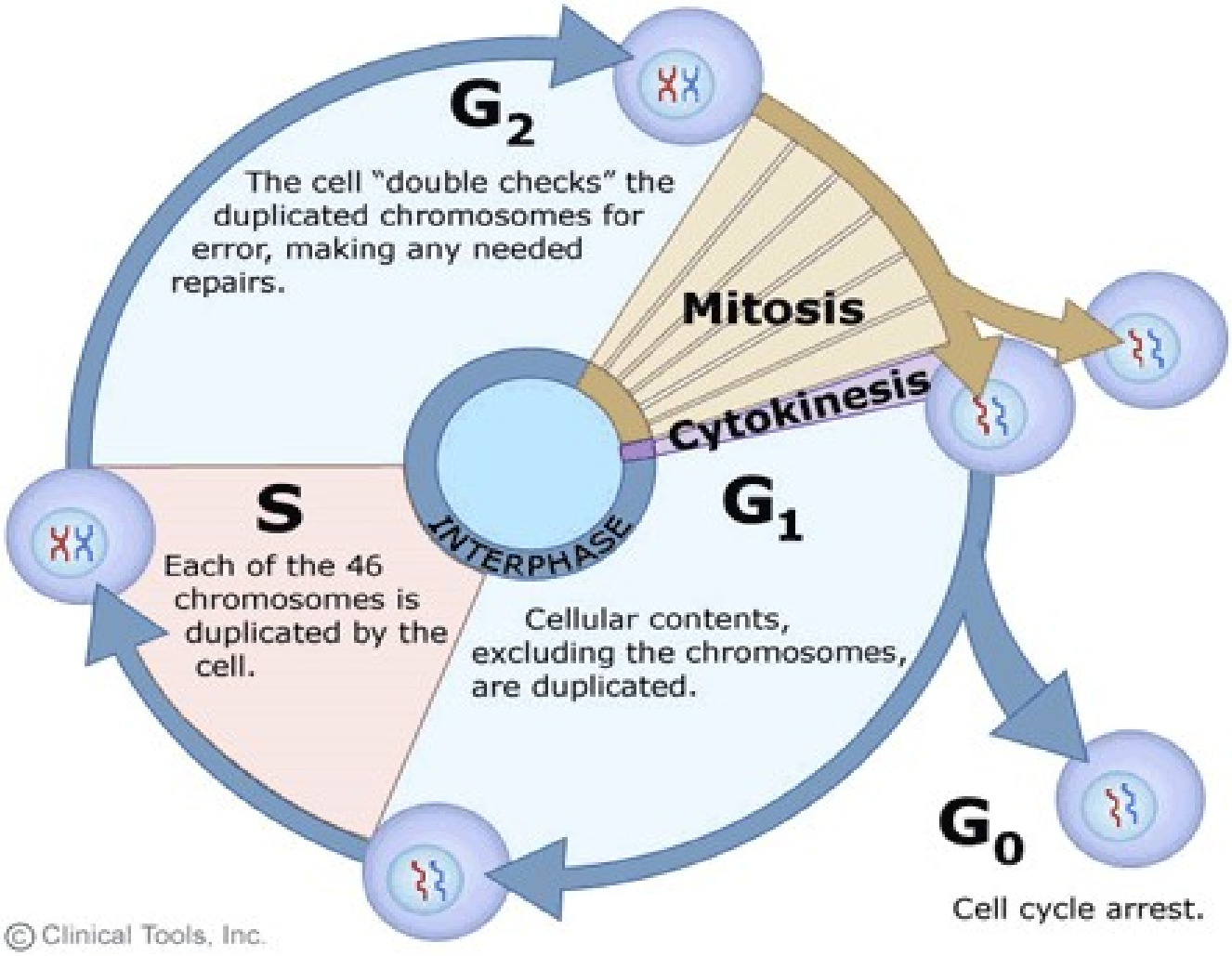
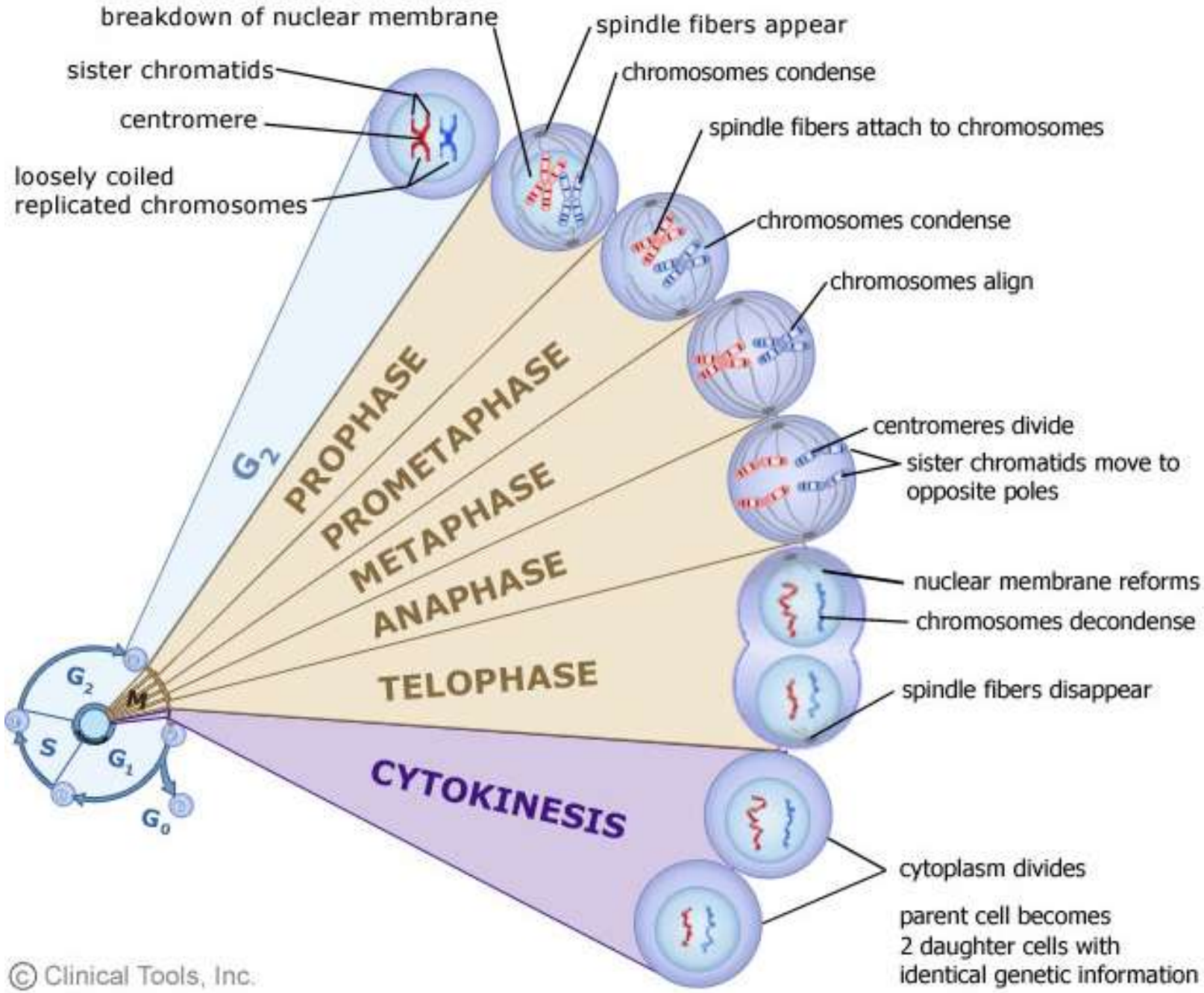


quiescent or arrested phase known as G0



Length of the cell cycle

- The length of the cell cycle is highly variable, even within the cells of a single organism.
- In humans, the frequency of cell turnover ranges from a few hours in early embryonic development, to an average of two to five days for epithelial cells, and to an entire human lifetime spent in G0 by specialized cells, such as cortical neurons or cardiac muscle cells.
- There is also variation in the time that a cell spends in each phase of the cell cycle. When fast-dividing mammalian cells are grown in culture (outside the body under optimal growing conditions), the length of the cycle is about 24 hours.
- In rapidly dividing human cells with a 24-hour cell cycle, the G1 phase lasts approximately nine hours, the S phase lasts 10 hours, the G2 phase lasts about four and one-half hours, and the M phase lasts approximately one-half hour.

- In early embryos of fruit flies, the cell cycle is completed in about eight minutes. The timing of events in the cell cycle is controlled by mechanisms that are both internal and external to the cell.

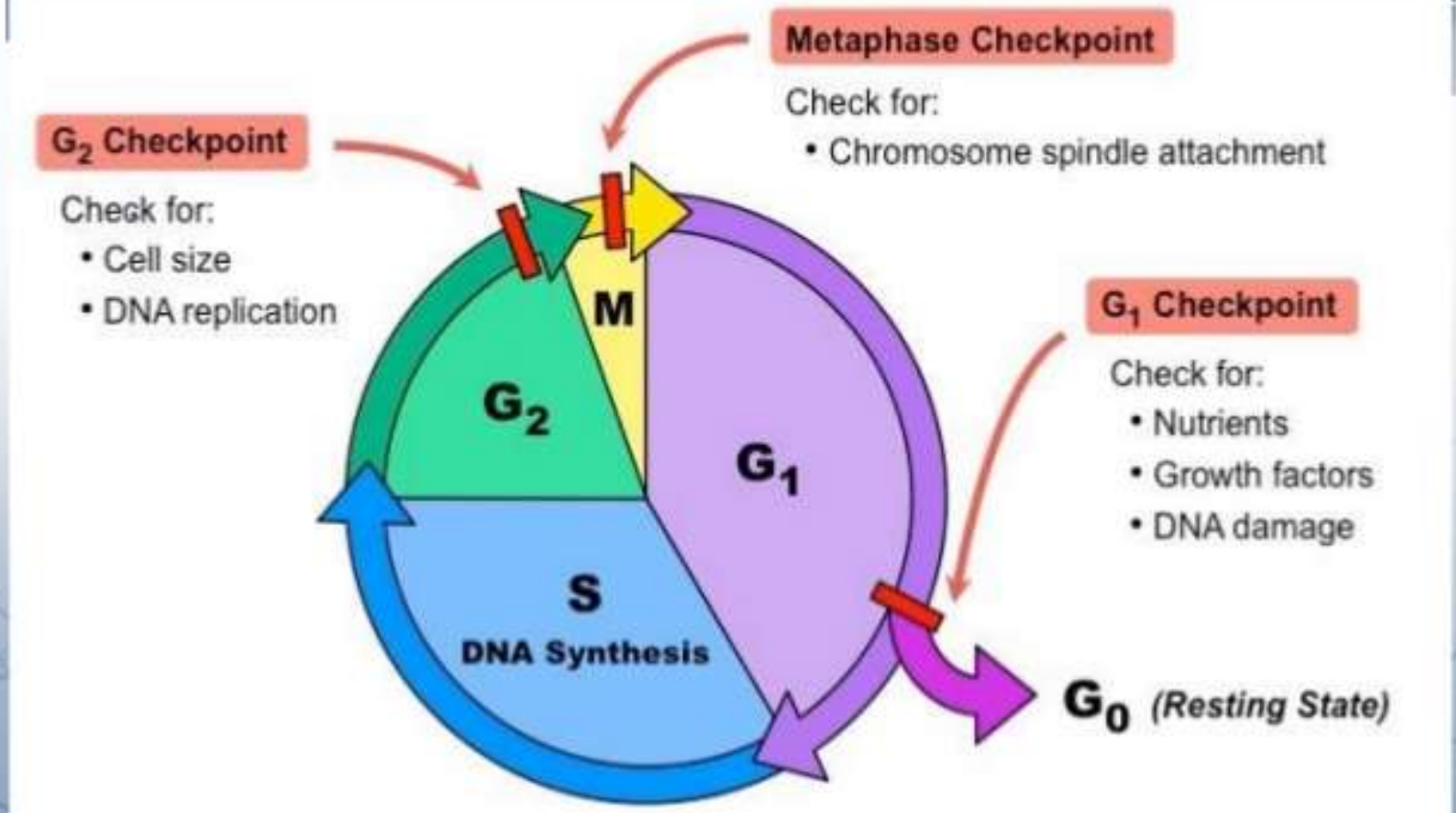
Cell cycle regulation

The current model of cell cycle regulation involves a highly conserved, genetically-controlled program that can be influenced by external signals

1. there are three major checkpoints, found in G1, G2 and mitosis---key regulatory components for checkpoints are cyclins and cyclin-dependent protein kinases
2. Cyclin-cell division proteins (their level increase or decrease depending upon cycle and cellular conditions

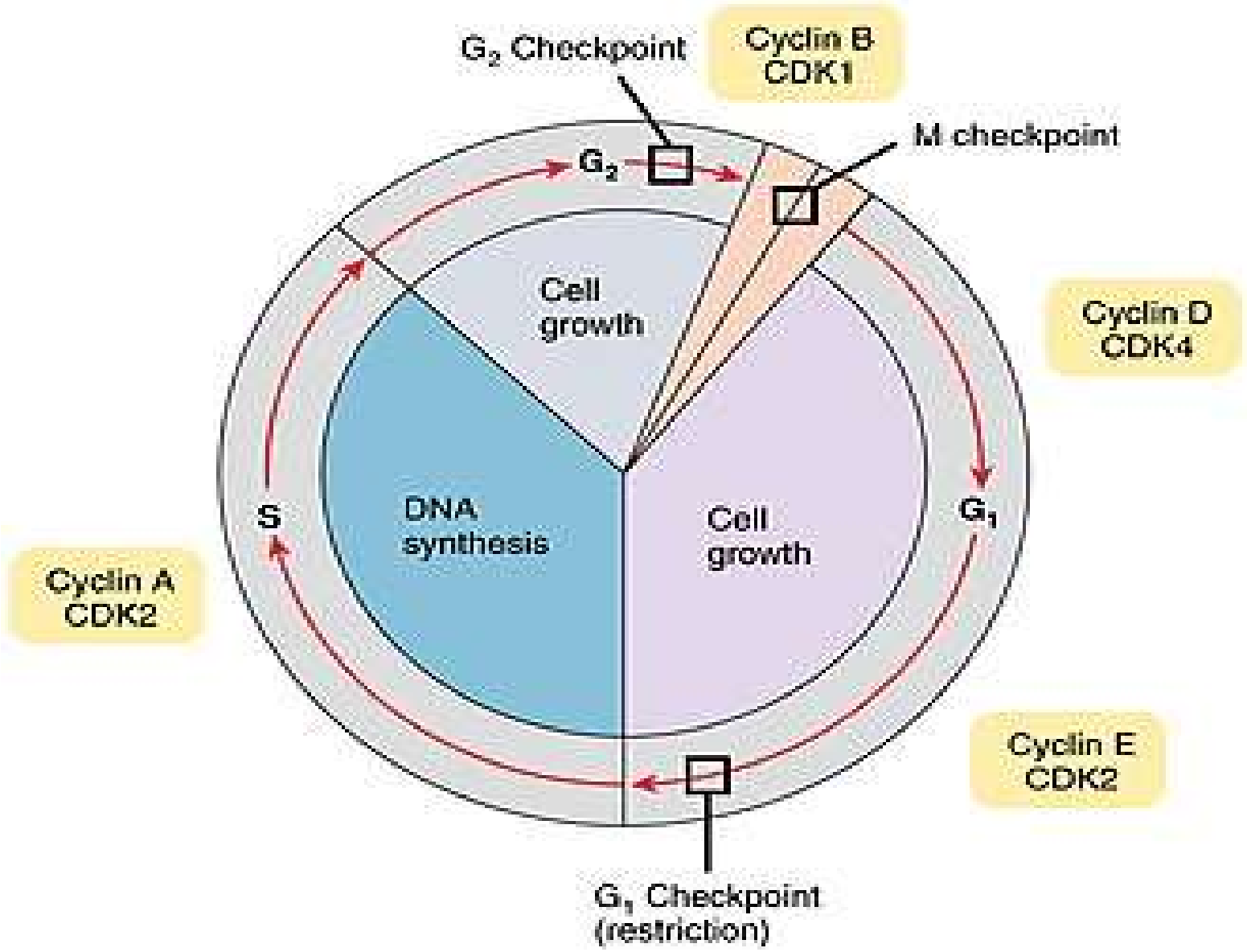
3. other factors can serve as suppressors of cell division(MPF-Mitosis promoting growth factor, PDGF-Platelets derived growth factors)
4. hormones such as **cytokinins** in plants, human growth hormone (HGH) and various protein growth factors in animals can stimulate progression through checkpoints in the right cells under the right conditions.
5. Density dependent inhibition or anchorage dependence

CHECKPOINTS



Checkpoints

The C. elegans genome encodes multiple members of the cyclin-dependent kinase (CDK) family.



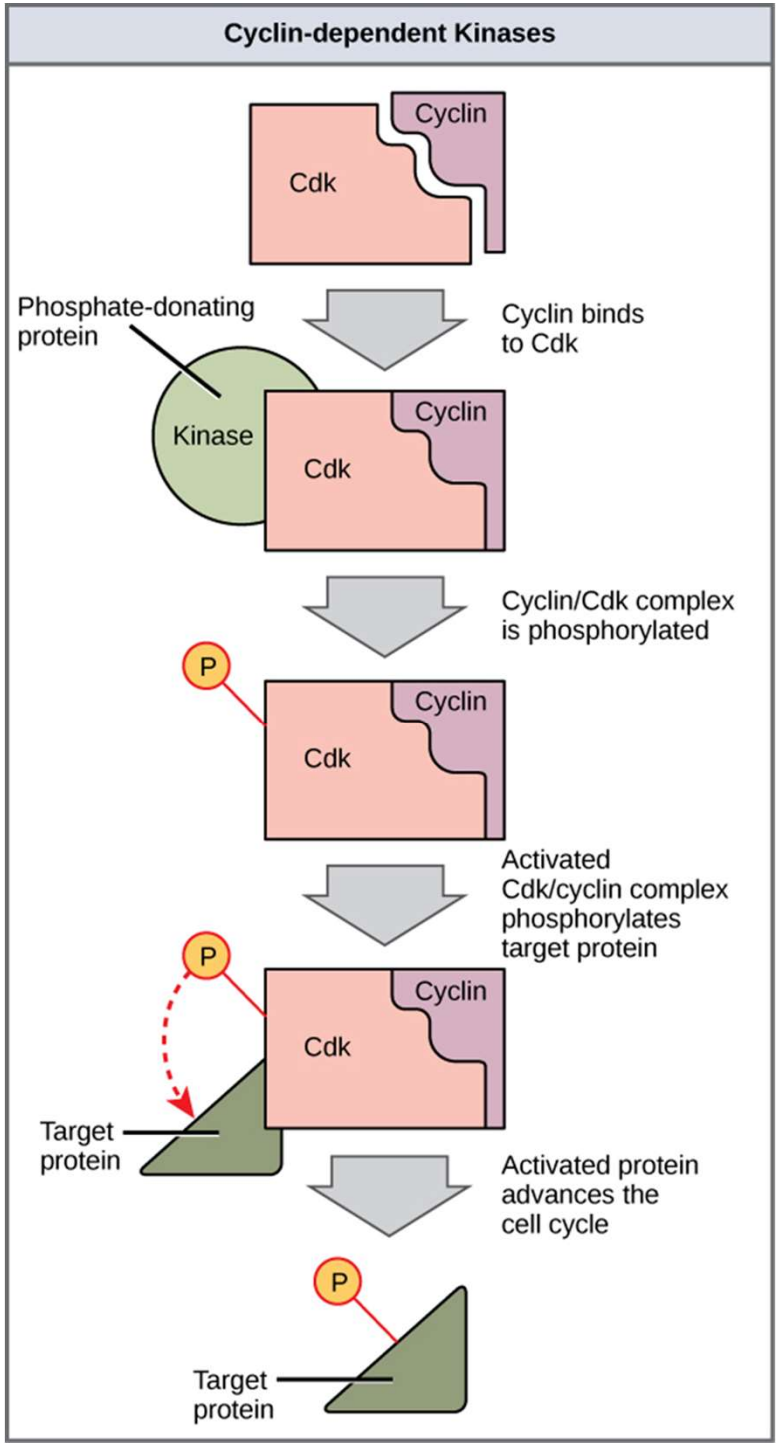
Cyclin and cyclin-dependent kinase (CDK)

- Cyclin is a family of proteins that controls the progression of a cell through the cell cycle by activating cyclin-dependent kinase (CDK) enzymes or group of enzymes required for synthesis of cell cycle.

"cyclin" was originally named by R. Timothy Hunt after his hobby cycling who discovered in 1982

- Cyclin-dependent kinases are the families of protein kinases first discovered for their role in regulating the cell cycle.
- They are also involved in regulating transcription, mRNA processing, and the differentiation of nerve cells.

Cyclin-dependent kinases (Cdks) are protein kinases that, when fully activated, can phosphorylate and thus activate other proteins that advance the cell cycle past a checkpoint. To become fully activated, a Cdk must bind to a cyclin protein and then be phosphorylated by another kinase.



Role of Cyclins

Cyclins bound with the dependent kinases, such as the p34/cdc2/cdk1 protein, form the maturation-promoting factor.

MPFs activate other proteins through phosphorylation.

These phosphorylated proteins, in turn, are responsible for specific events during cycle division such as microtubule formation and chromatin remodeling.

Classification of Cyclins

1. G1 cyclins (D)----G1/S Cyclins rise in late G1 and fall in early S phase.
2. G1/S cyclins (E)
3. S cyclins (A)
4. M cyclins (B)

G1 cyclins do not behave like the other cyclins
It coordinate cell growth with the entry to a new cell cycle

G1/S Cyclins & Cdk- G1/S cyclin complex

- G1/S Cyclins rise in late G1 and fall in early S phase.
- Cdk- G1/S cyclin complex begins to induce the initial processes of DNA replication, primarily by arresting systems that prevent S phase Cdk activity in G1.
- The cyclins also promote other activities to progress the cell cycle, such as centrosome duplication in vertebrates or spindle pole body in yeast.

S cyclins

S cyclins bind to Cdk and the complex directly induces DNA replication.

The levels of S cyclins remain high, not only throughout S phase, but through G2 and early mitosis as well to promote early events in mitosis

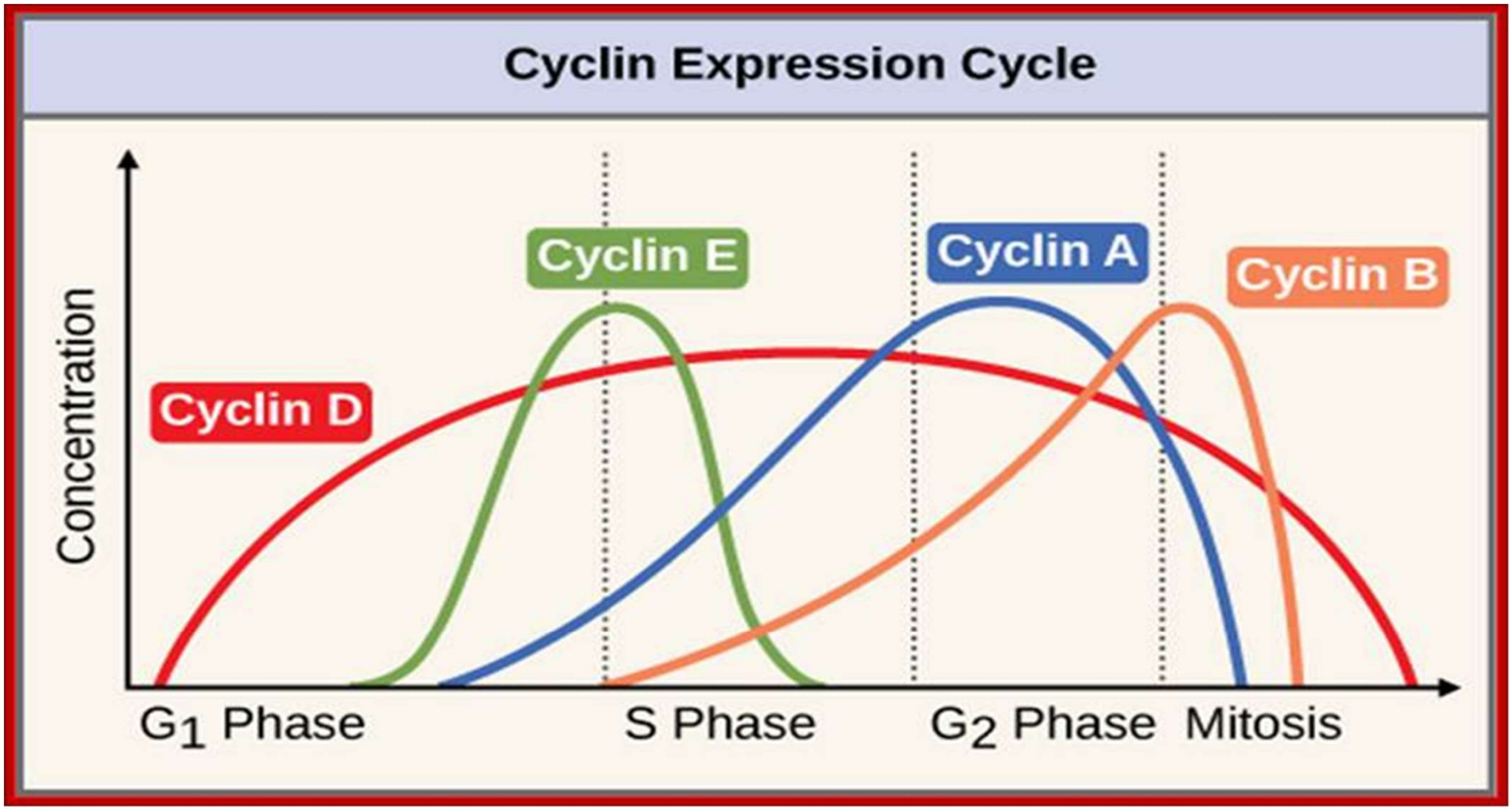
M cyclin

- M cyclin concentrations rise as the cell begins to enter mitosis and the concentrations peak at metaphase.
- Cell changes in the cell cycle like the assembly of mitotic spindles and alignment of sister-chromatids along the spindles are induced by M cyclin- Cdk complexes.
- The destruction of M cyclins during metaphase and anaphase, after the Spindle Assembly Checkpoint is satisfied, causes the exit of mitosis and cytokinesis.

Main groups

There are two main groups of cyclins:

- G_1/S cyclins – essential for the control of the cell cycle at the G_1/S transition,
  - Cyclin A / CDK2 – active in S phase.
  - Cyclin D / CDK4, Cyclin D / CDK6, and Cyclin E / CDK2 – regulates transition from G_1 to S phase.
- G_2/M cyclins – essential for the control of the cell cycle at the G2/M transition (mitosis). G_2/M cyclins accumulate steadily during G_2 and are abruptly destroyed as cells exit from mitosis (at the end of the M-phase).
  - Cyclin B / CDK1 – regulates progression from G_2 to M phase.



Expression of human cyclins through the cell cycle

Mitosis-promoting factor (maturation-promoting factor; MPF)

- MPF: A protein complex responsible for triggering mitosis in somatic cells and for maturation of oocytes into egg cells.

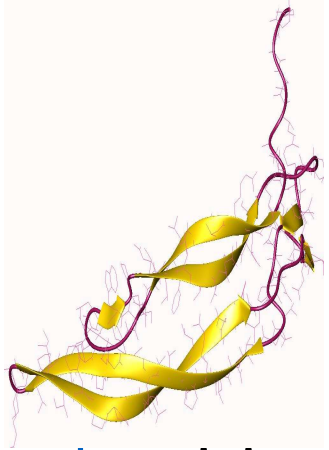
- It contain Cyclin bounded to enzyme CDK kinase
- cyclin-Cdk complex stimulates the mitotic and meiotic phases of the cell cycle. MPF promotes the entrance into mitosis from the G_2 phase by phosphorylating multiple proteins needed during mitosis.

Role of MPF

- condensation of chromosomes
- formation of the mitotic spindle
- breakdown of the nuclear envelope

Levels of cyclins and MPF rise as the cell enters mitosis, reach a peak during mitosis, and then fall during anaphase.

Platelet-derived growth factor (PDGF)



- It regulate cell growth and division.
- PDGF is a potent mitogen for cells of mesenchymal origin, including fibroblasts, smooth muscle cells and glial cells.

- PDGF plays a role in embryonic development, cell proliferation, cell migration, and angiogenesis.
- Over-expression of PDGF has been linked to several diseases such as atherosclerosis, fibrotic disorders and malignancies.

Cytokinins & human growth hormone (HGH)

- Cytokinins are involved in many plant processes, including cell division and shoot and root morphogenesis. ... This promotes shoot growth, and restricts lateral branching.

- Cytokinin moves from the roots into the shoots, eventually signaling lateral bud growth.

Human growth hormone

- A lack of **HGH** can inhibit cell division, resulting in dwarfism, whereas too much HGH can result in gigantism. Crowding of cells can also inhibit cell division. Another factor that can initiate cell division is the size of the cell; as a cell grows, it becomes inefficient due to its decreasing surface-to-volume ratio.

- **Density-Dependent Inhibition**?

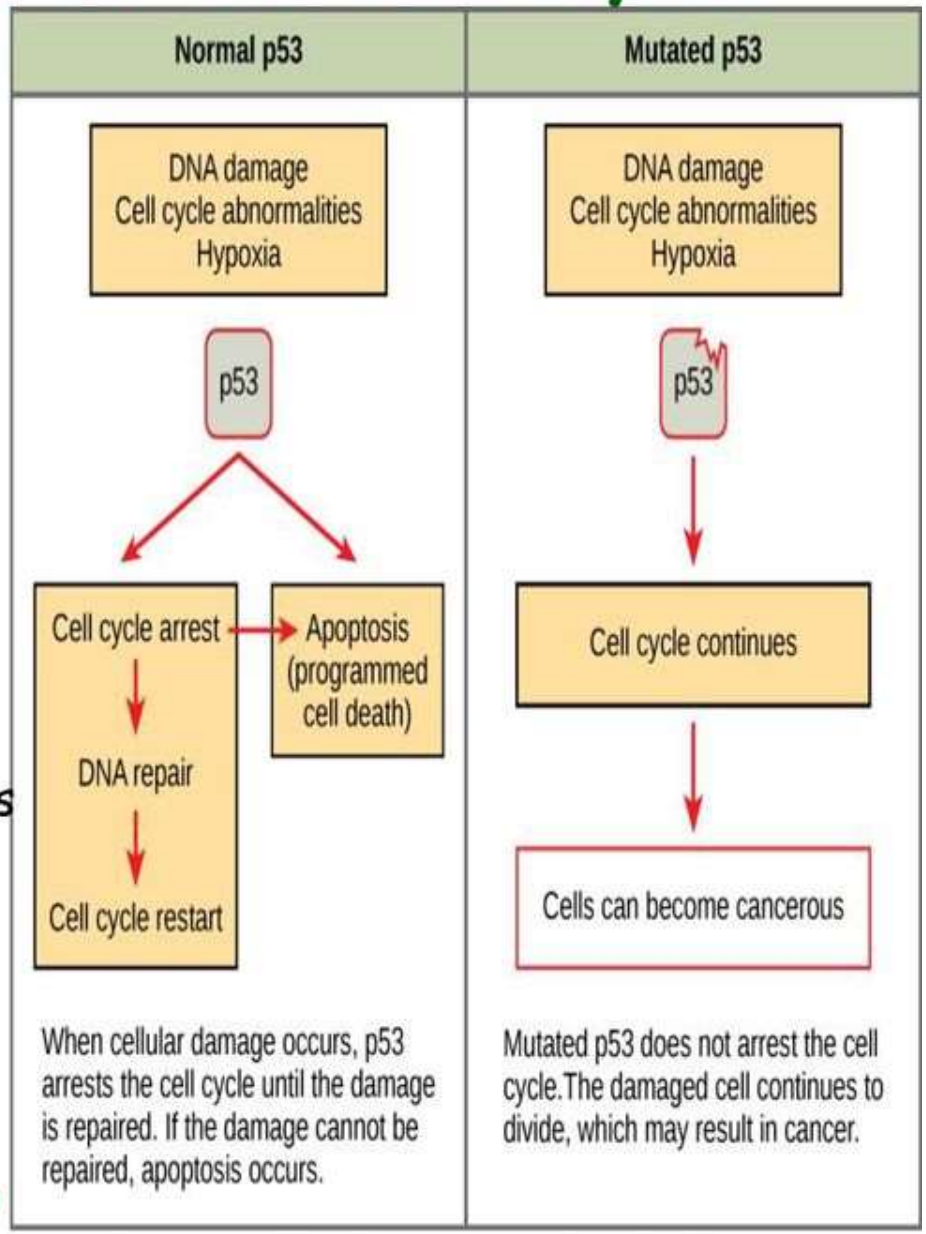
If a cell is crowded it will not divide. Cells will stop dividing when they are in contact with others cells.

Anchorage dependence refers to the need for cells to be adhered to or in contact with another layer of cells. The cells can be adhered to other cells, extracellular matrix, or tissue culture plastic (via proteins). In any manner, many cell types require some sort of anchorage in order to survive. Therefore, if an anchorage dependent cell is not adhered and floating around, it will die

Negative Regulation of the Cell Cycle

Retinoblastoma proteins:

- A group of tumor-suppressor proteins common in many cells.
  - *Act primarily at the G1 checkpoint.*
- p53 is a multi-functional protein that has a major impact on the commitment of a cell to division
- Acts when there is damaged DNA in cells that are undergoing G_1.
- If damaged DNA is detected, p53 halts the cell cycle and recruits enzymes to repair the DNA.
- If the DNA cannot be repaired, p53 can trigger apoptosis
- *Mutated p53 induces cancer formation*



Negative regulators of cell cycle

- **G1 cyclins** do not behave like the other cyclins

- It coordinate cell growth with the entry to a new cell cycle

Negative regulators

- (retinoblastoma protein) Rb, p53, and p21 act primarily at the G_1 checkpoint.
- Retinoblastoma proteins are a group of tumor-suppressor proteins common in many cells.
- p53 is a multi-functional protein that has a major impact on the commitment of a cell to division because it acts when there is damaged DNA in cells that are undergoing the preparatory processes during G_1. If damaged DNA is detected, p53 halts the cell cycle and recruits enzymes to repair the DNA. If the DNA cannot be repaired, p53 can trigger apoptosis, or cell suicide, to prevent the duplication of damaged chromosomes. As p53 levels rise, the production of p21 is triggered.

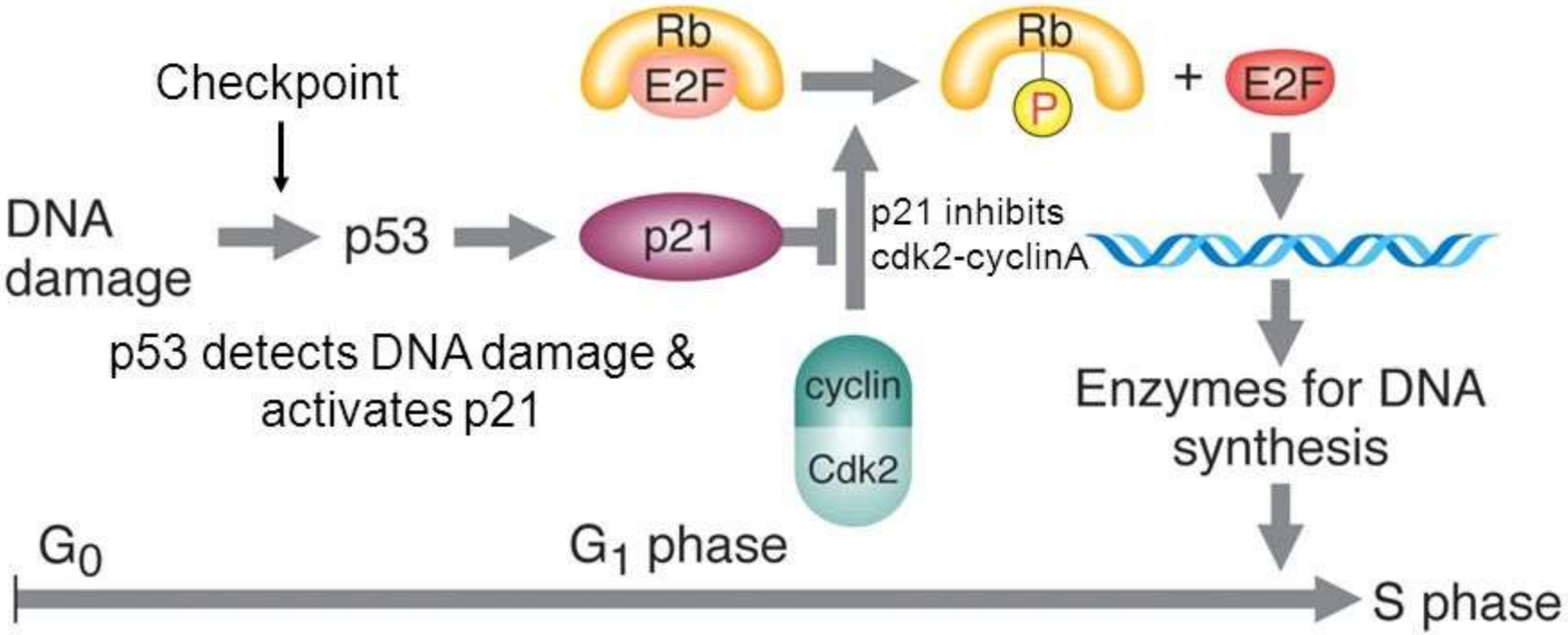
p21

- The 53 and 21 designations refer to the functional molecular masses of the proteins (p) in kilodaltons. Much of what is known about cell cycle regulation comes from research conducted with cells that have lost regulatory control.

- p21 enforces the halt in the cycle dictated by p53 by binding to and inhibiting the activity of the Cdk/cyclin complexes. As a cell is exposed to more stress, higher levels of p53 and p21 accumulate, making it less likely that the cell will move into the S phase.

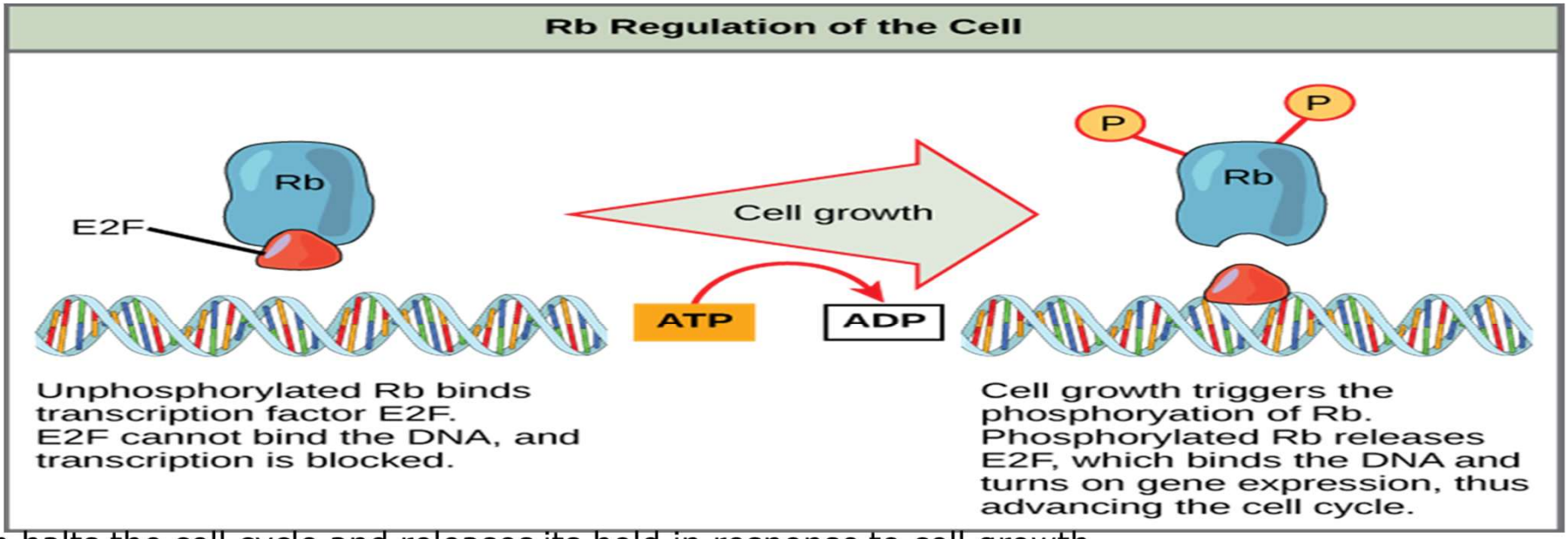
Intracellular Regulation of Cell Cycle & Apoptosis

Negative regulation of cell cycle by intracellular signals



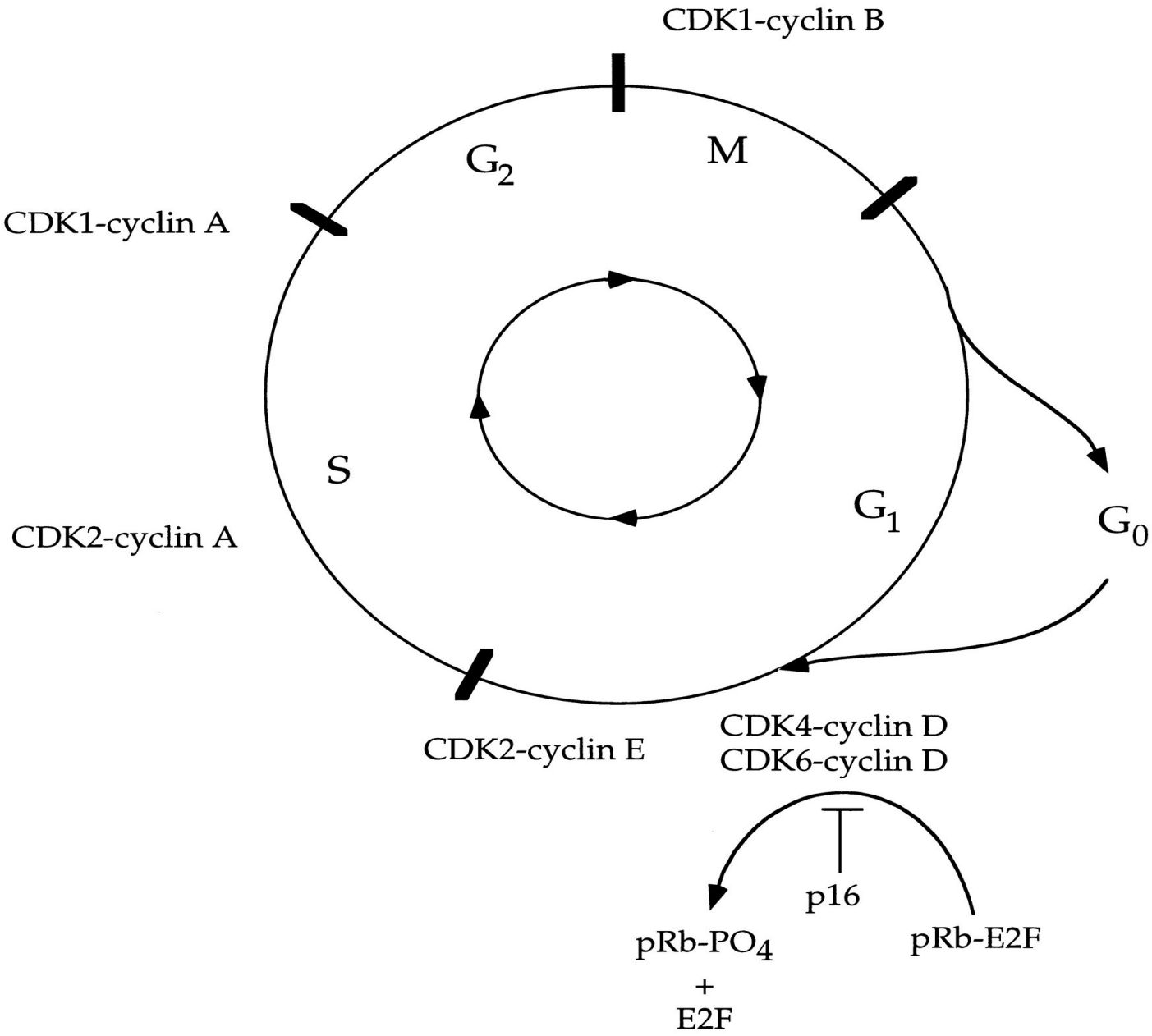
Checkpoints: block cell from proceeding through cell cycle if cell is damaged.

- Rb exerts its regulatory influence on other positive regulator proteins.
- Chiefly, Rb monitors cell size. In the active, dephosphorylated state, Rb binds to proteins called transcription factors, most commonly, E2F (Figure) Transcription factors “turn on” specific genes, allowing the production of proteins encoded by that gene. When Rb is bound to E2F, production of proteins necessary for the G_1/S transition is blocked. As the cell increases in size, Rb is slowly phosphorylated until it becomes inactivated. Rb releases E2F, which can now turn on the gene that produces the transition protein, and this particular block is removed. For the cell to move past each of the checkpoints, all positive regulators must be “turned on,” and all negative regulators must be “turned off.”



Rb halts the cell cycle and releases its hold in response to cell growth.

Rb and other proteins that negatively regulate the cell cycle are sometimes called tumor suppressors


CDK1-cyclin B
G2
M
CDK1-cyclin A
S
G1
G0
CDK2-cyclin A
CDK2-cyclin E
CDK4-cyclin D
CDK6-cyclin D
p16
pRb-PO4
+
E2F
pRb-E2F