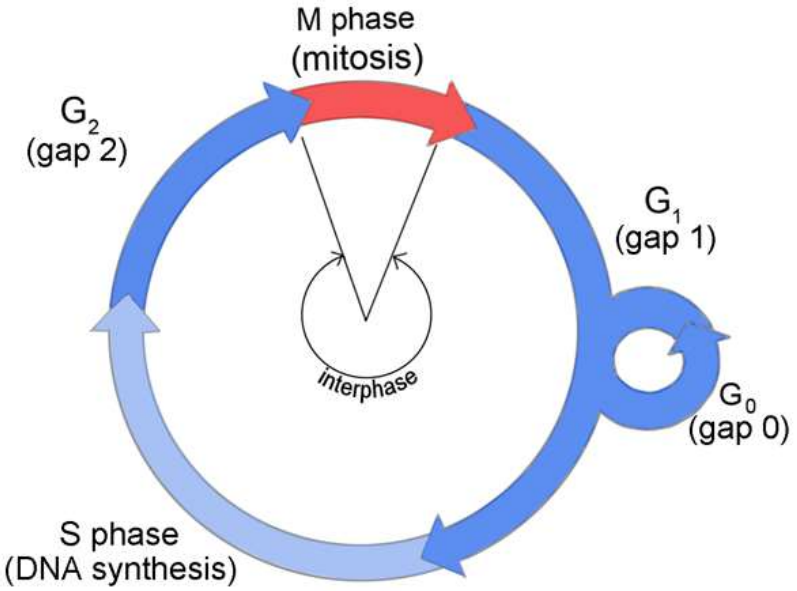
Cell Cycle & Its Regulation



Dr. Barnali Ray Basu
Assistant Professor
Department of Physiology
Surendranath College

CELL CYCLE

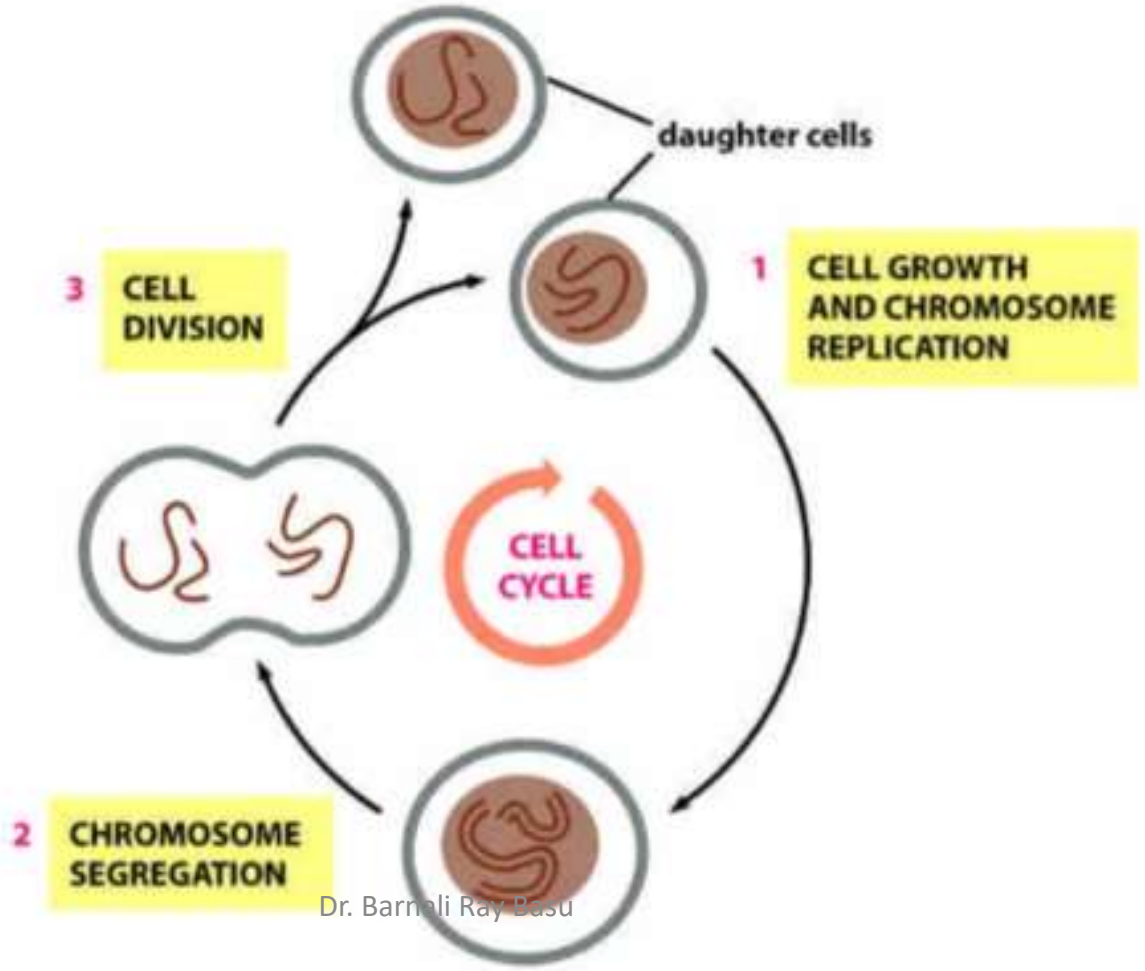
When a cell has grown to its maximum size it divides , and it take place a series of changes in a newly formed cell which involve in growth and division to form 2 daughter cells , it is called Cell cycle.

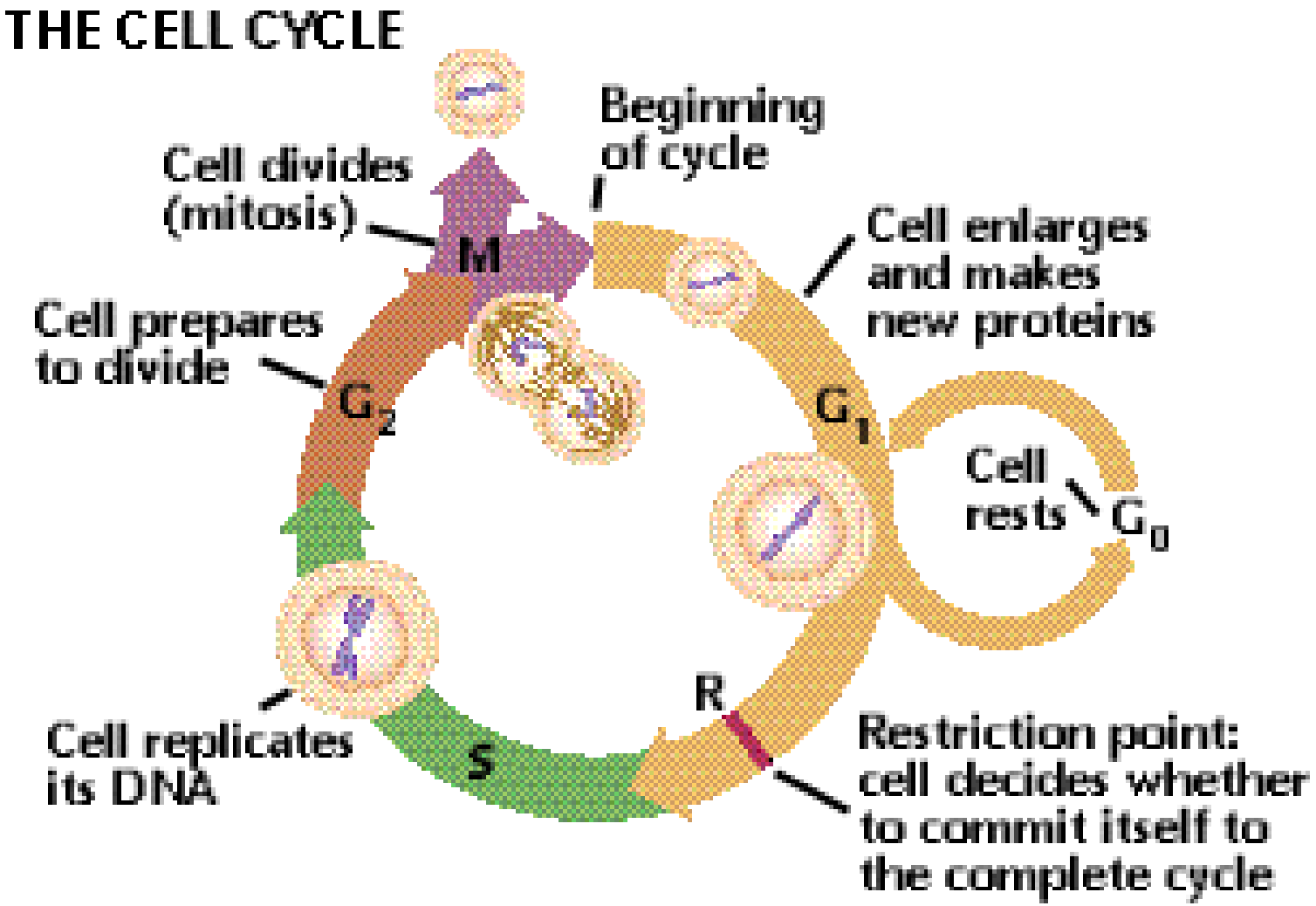
It consist of two stages,

- **A non dividing growing Interphase Or I Phase**
- **A Short Dividing Mitotic/ M Phase**

Cell cycle

A cell reproduces by performing an orderly sequence of events in which it duplicates its contents and then divides in two




THE CELL CYCLE
Beginning of cycle
Cell divides (mitosis)
M
Cell enlarges and makes new proteins
Cell prepares to divide
G2
G1
Cell rests
G0
R
Cell replicates its DNA
S
Restriction point: cell decides whether to commit itself to the complete cycle

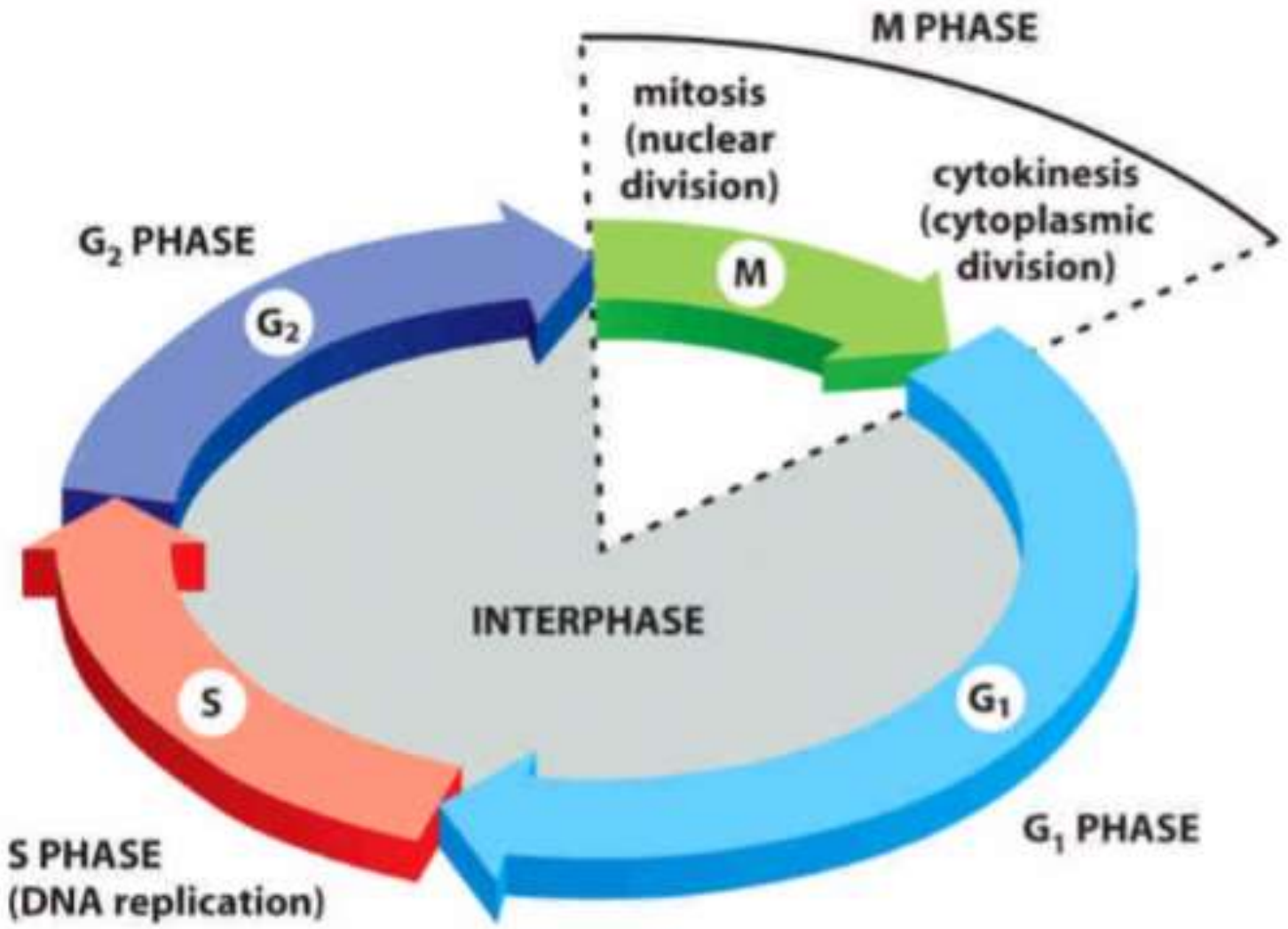
INTERPHASE

- The period between **two mitotic divisions** is called **Interphase .**

It is further divisible into 3 stages:

1. **G1 phase**
2. **S phase**
3. **G2 phase**

The phases of cell cycle



G1 phase :

- It is the **post mitotic phase** and takes place at the end of cell division the newly formed cells accumulate the energy and prepares themselves for the synthesis of DNA . During this **, active synthesis of RNA and protein** takes place .

S phase :

It is the **synthesis phase** during this phase **duplication of DNA and centriole** takes places. The duplication of DNA results in the duplication of chromosomes .

G2 phase :

It is the **pre- mitotic gap** phase (invisible phase) the synthesis of RNA and protein continues in this phase. The **formation of macro molecules** for spindle formation takes place and the cell prepare it self to go into the mitotic phase .

MITOTIC PHASE

M Phase follows the interphase. This last for a shot period compare to interphase .During this phase two important processes occur simultaneously they are

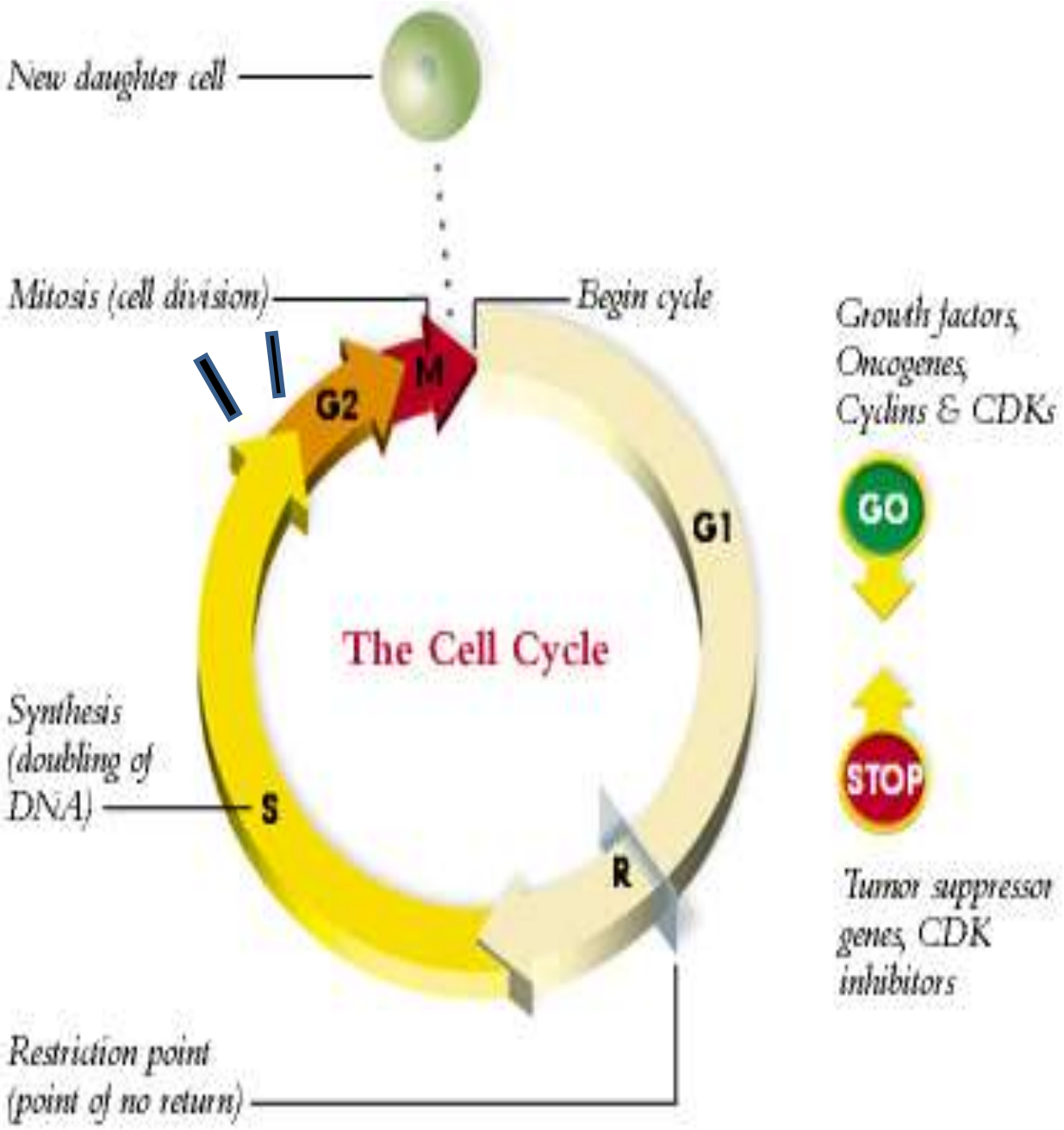
karyokinesis (division of nucleus) :

It results in the separation of chromosomes into two equal groups .

Cytokinesis (division of cytoplasm) :

It results in division of cytoplasmic components into approximately two halves.

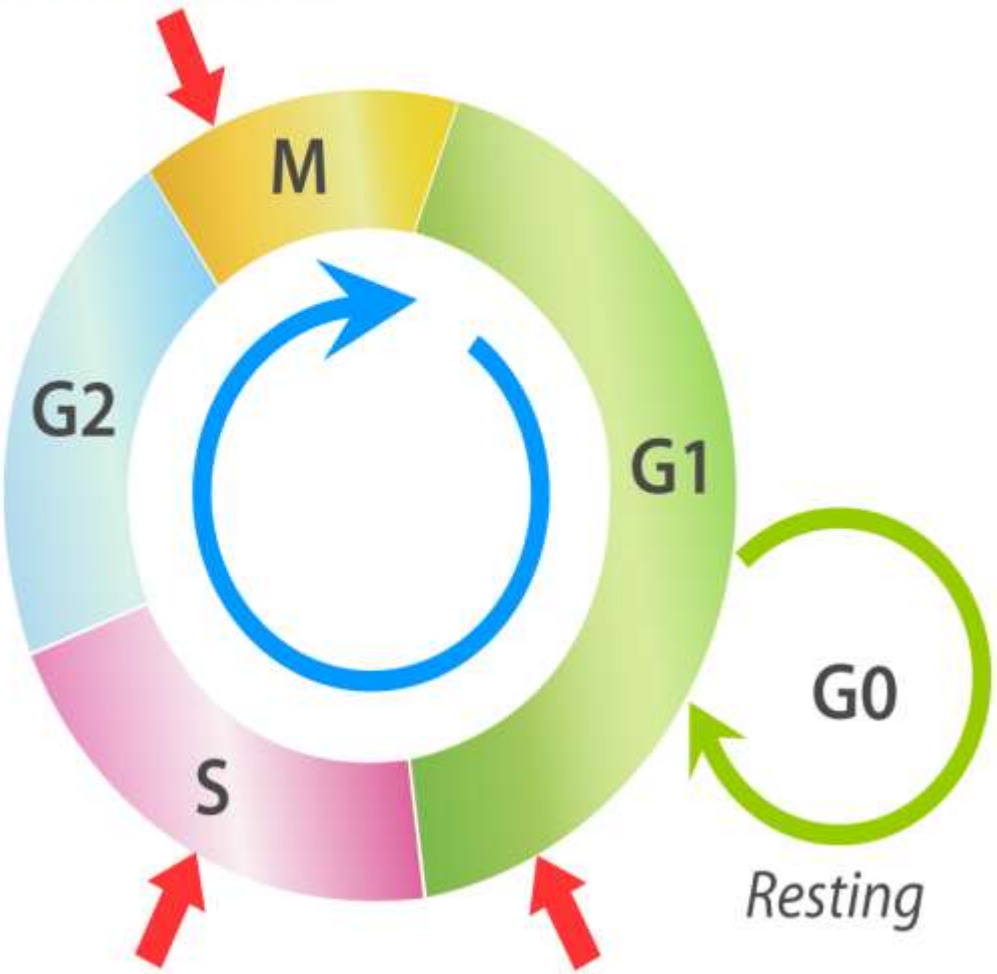
After M phase a cell may either enter interphase to repeat the cell cycle or G0 phase to arrest the cell cycle. The cells in G0 phase may grow in size and get differentiated .



A checkpoint in the cell cycle is a critical control point where stop and go signals regulate the cycle.

3 major checkpoints are found in the G1, G2, and M phases.

The Cell Cycle and the Checkpoints



1. Cell Growth Checkpoint

- Occurs toward the end of growth phase 1 (G1).
- Checks whether the cell is big enough and has made the proper proteins for the synthesis phase.
- If not, the cell goes through a resting period (G0) until it is ready to divide.

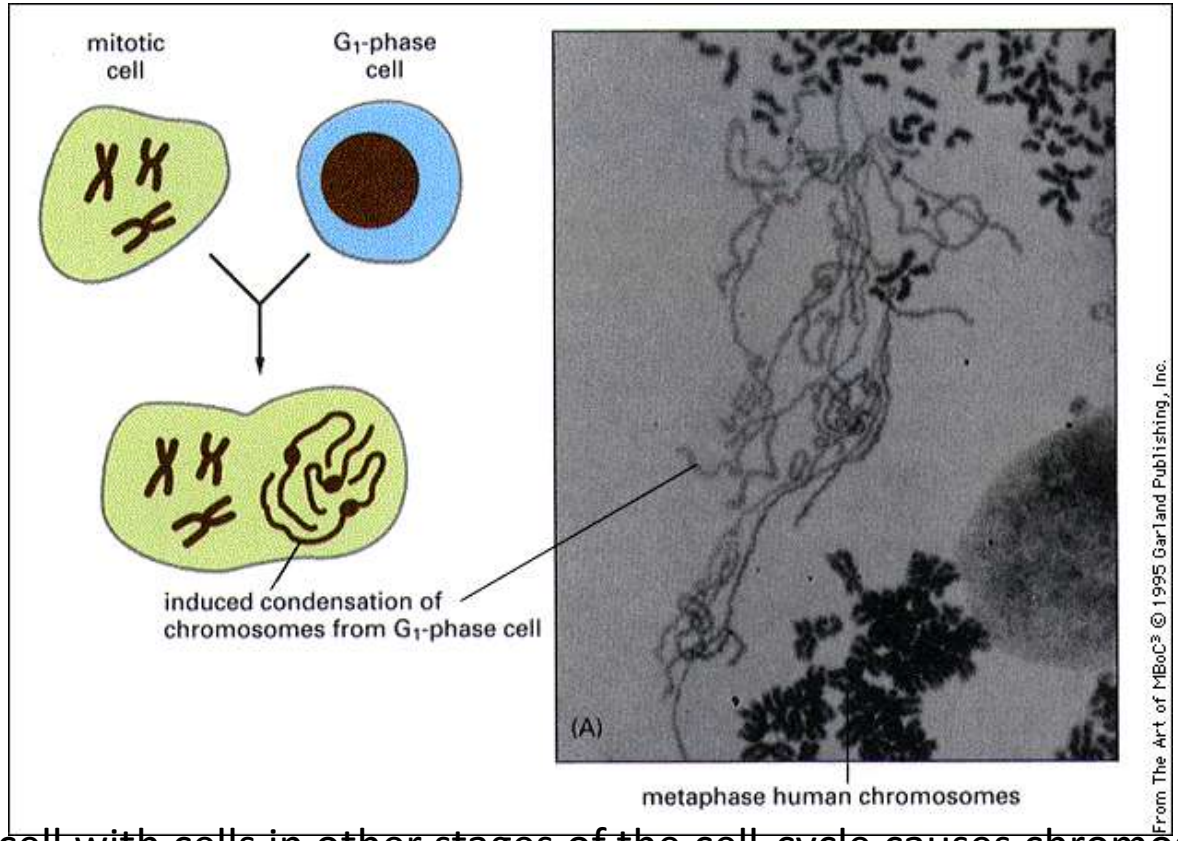
2. DNA Synthesis Checkpoint

- Occurs during the synthesis phase (S).
- Checks whether DNA has been replicated correctly
- If so, the cell continues on to mitosis (M).

3. Mitosis Checkpoint

- Occurs during the mitosis phase (M).
- Checks whether mitosis is complete.
- If so, the cell divides, and the cycle repeats.

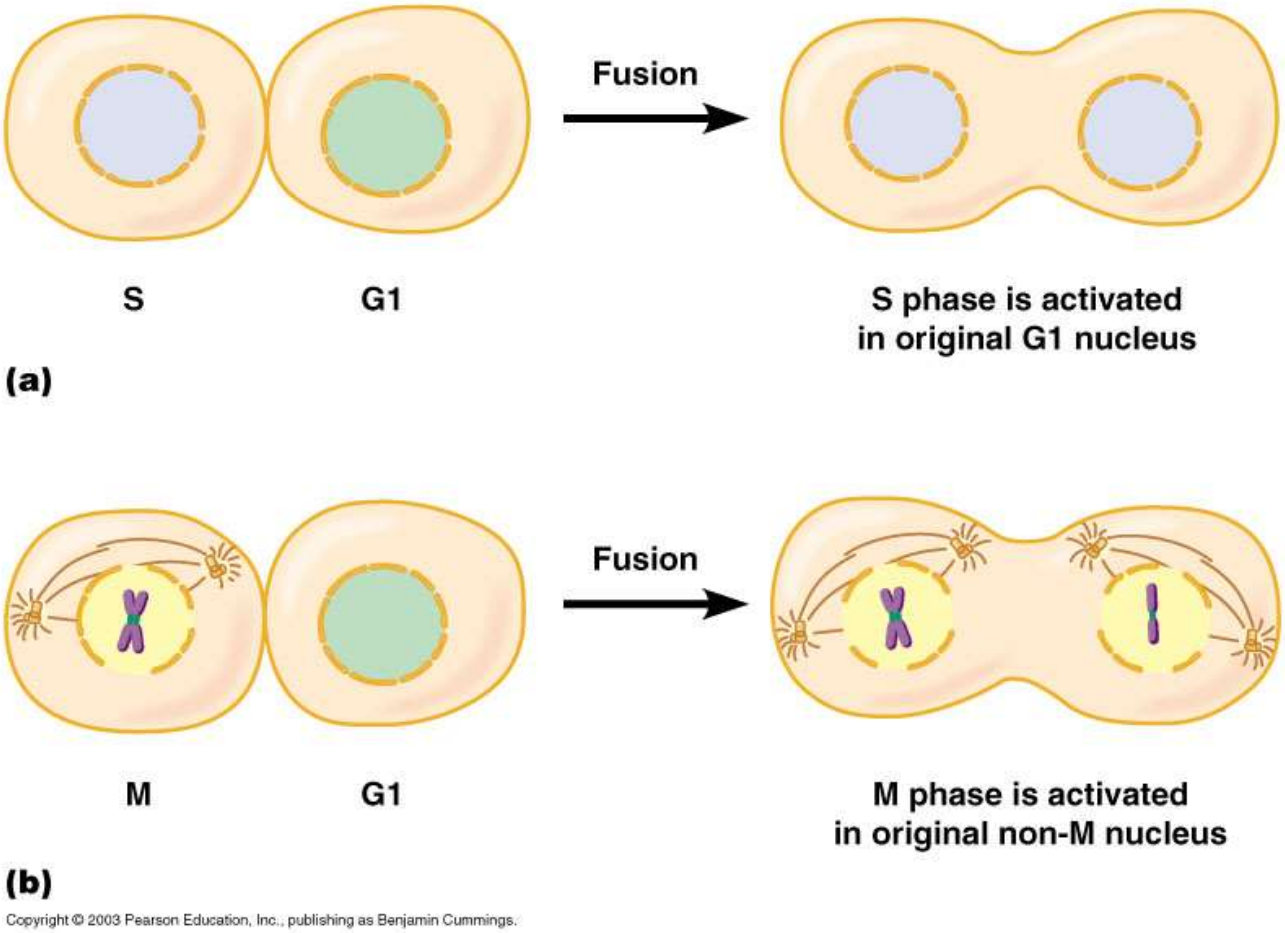
MITOSIS PROMOTING FACTOR (MPF)



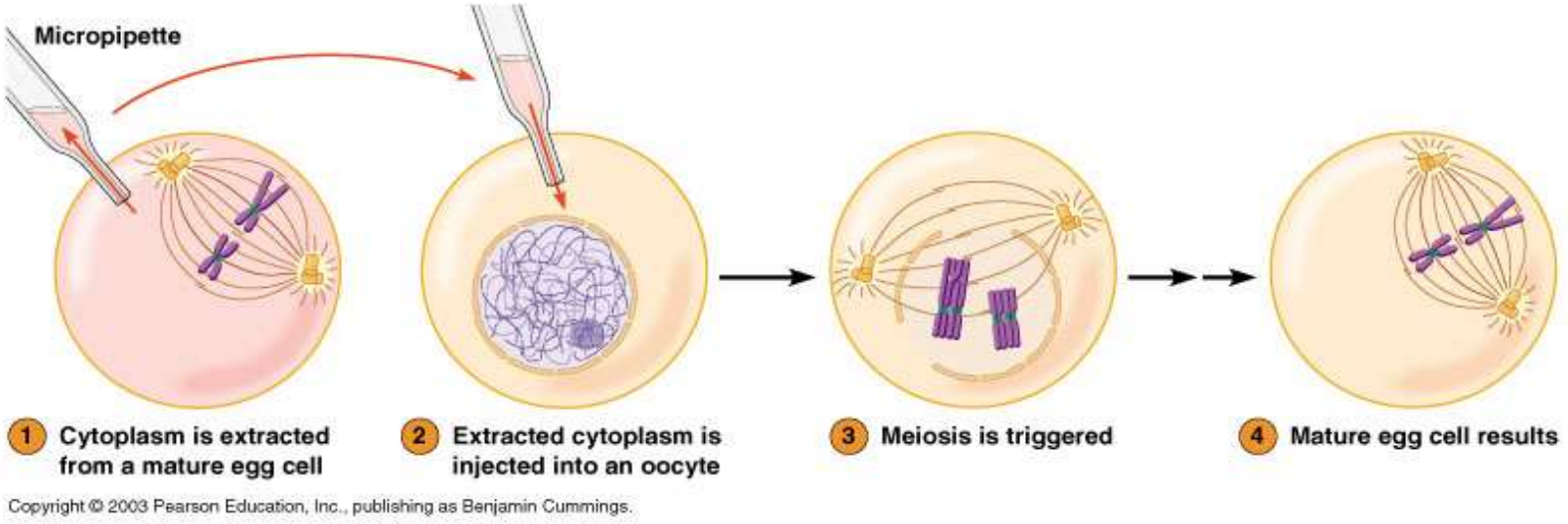
Fusion of mitotic cell with cells in other stages of the cell-cycle causes chromosomes of the other cell to condense and the nucleus to breakdown.

Mitotic cells must contain a mitosis -promoting factor (MPF) – produced at the end of G2?

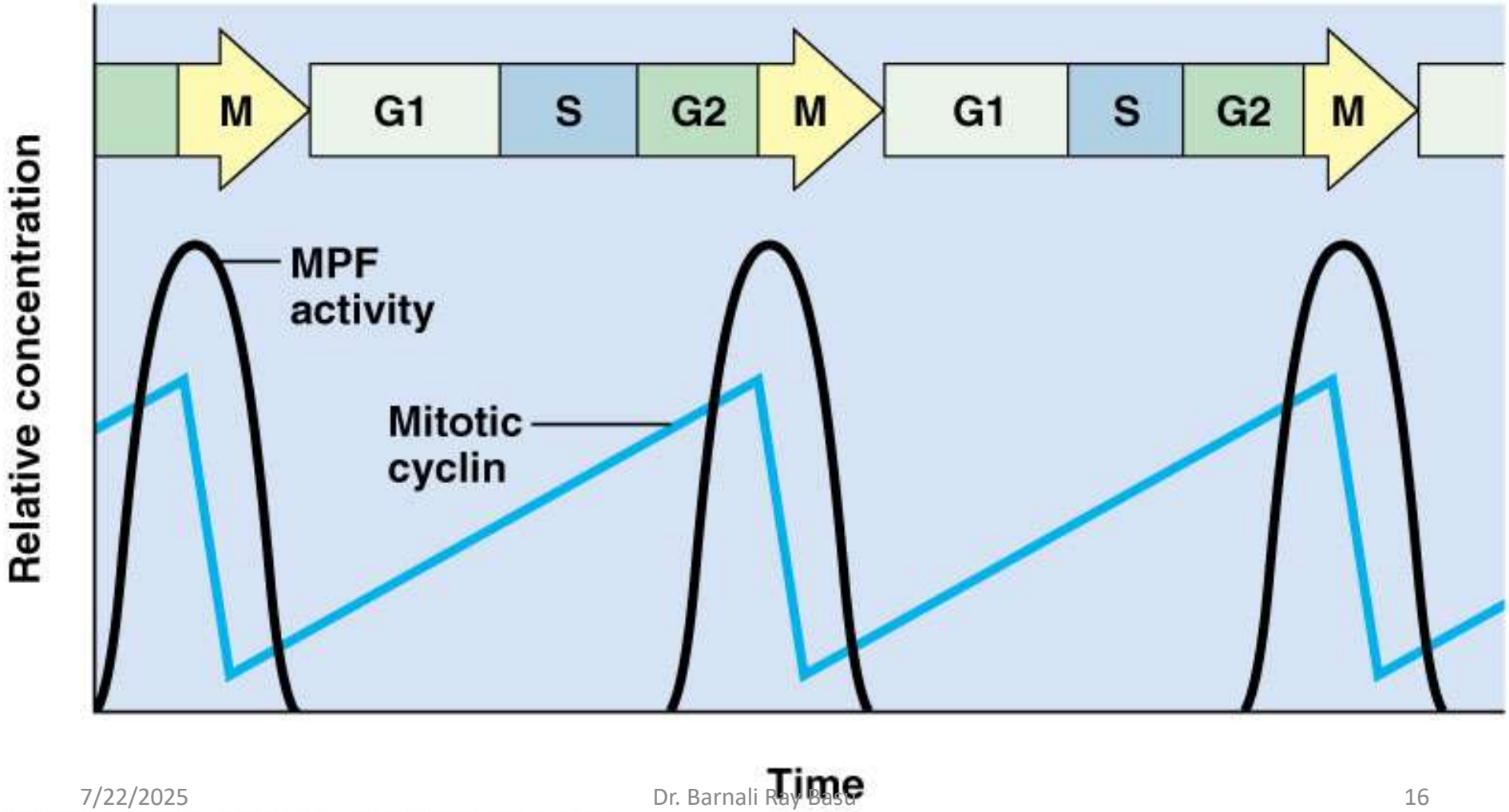
Evidence that Cytoplasmic Signals Control the Cell Cycle



Evidence for a Maturation (or Mitosis) Promoting Factor (MPF) – Masui et al. 1971



Synthesis and Degradation of Cyclin correlates with MPF Activity



Cell Division Cycle (cdc) Mutants in Yeast (late 1980's)

- Hartwell (Nobel Prize, 2001) et al., working with budding yeast *S. cerevisiae*
  - Found temperature-sensitive mutants stuck in some point of cell cycle
- Nurse (Nobel Prize, 2001) et al., working with fission yeast *S. pombe*
  - Found gene they called cdc2, essential for passing G2 checkpoint
  - cdc2 turned out to be a new protein kinase - cyclin dependant kinase (Cdk) - with counterparts in all eukaryotic cells.

CONTROL OF THE CELL CYCLE

Three checkpoints:

- The **G1/S cell cycle checkpoint**
- **G2/M DNA damage checkpoint**
- **Mitosis checkpoint**

G1/S cell cycle checkpoint

controls the passage of eukaryotic cells from the first 'gap' phase (G1) into the DNA synthesis phase (S).

Checks:

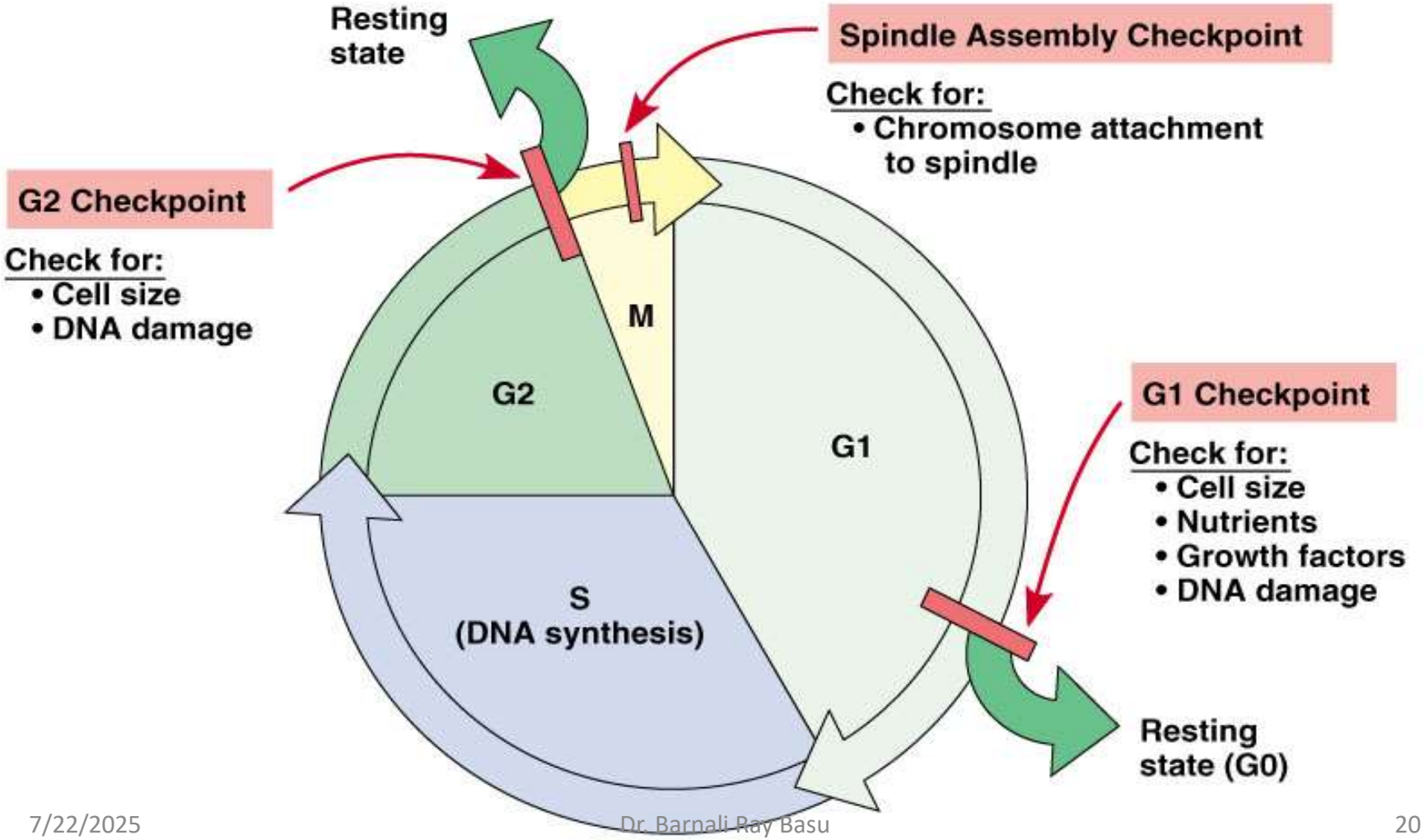
That the size is CORRECT

That the environment is CORRECT

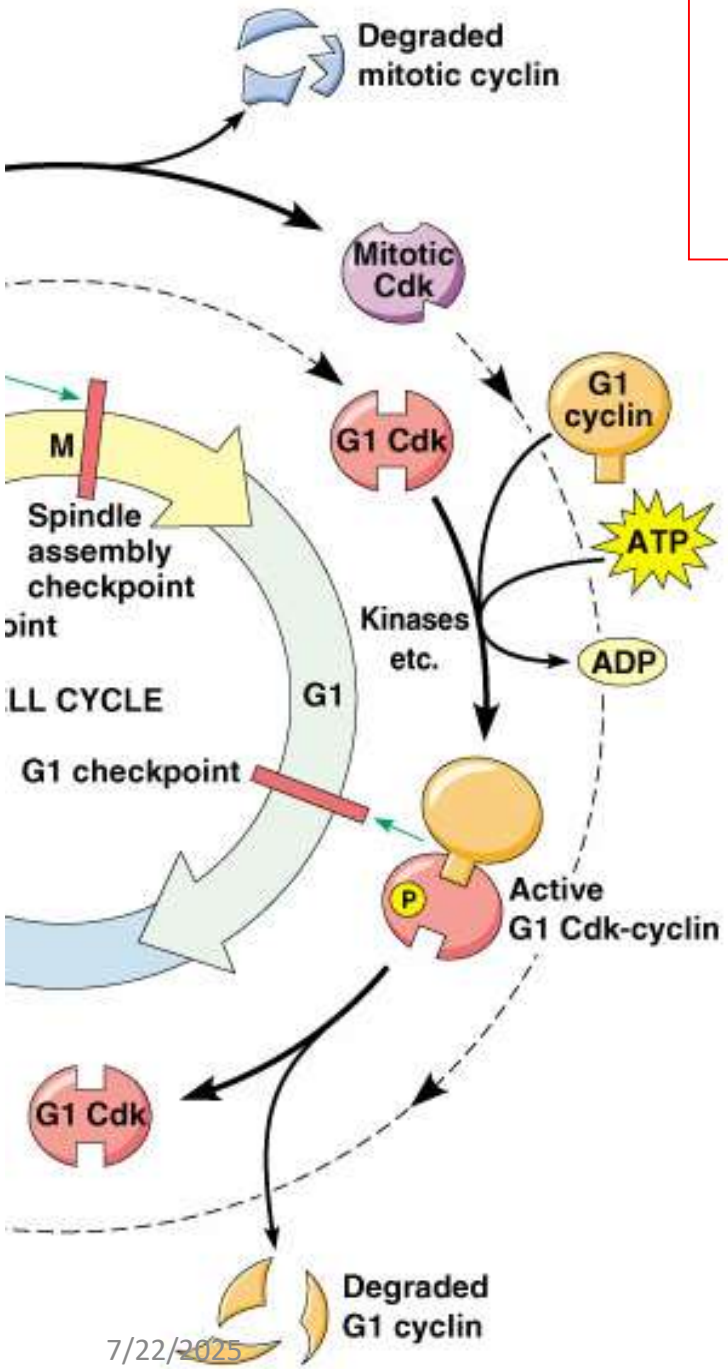
External agents regulate progression

Kinases – add a phosphate group (phosphorylate)

Regulation of the Cell Cycle: Cell Cycle Checkpoints



G1 checkpoint



- Controlled by G1 Cdks-cyclin
- G1 cyclin levels also vary with the cell cycle
- Many additional levels of phosphorylation, dephosphorylation regulate.

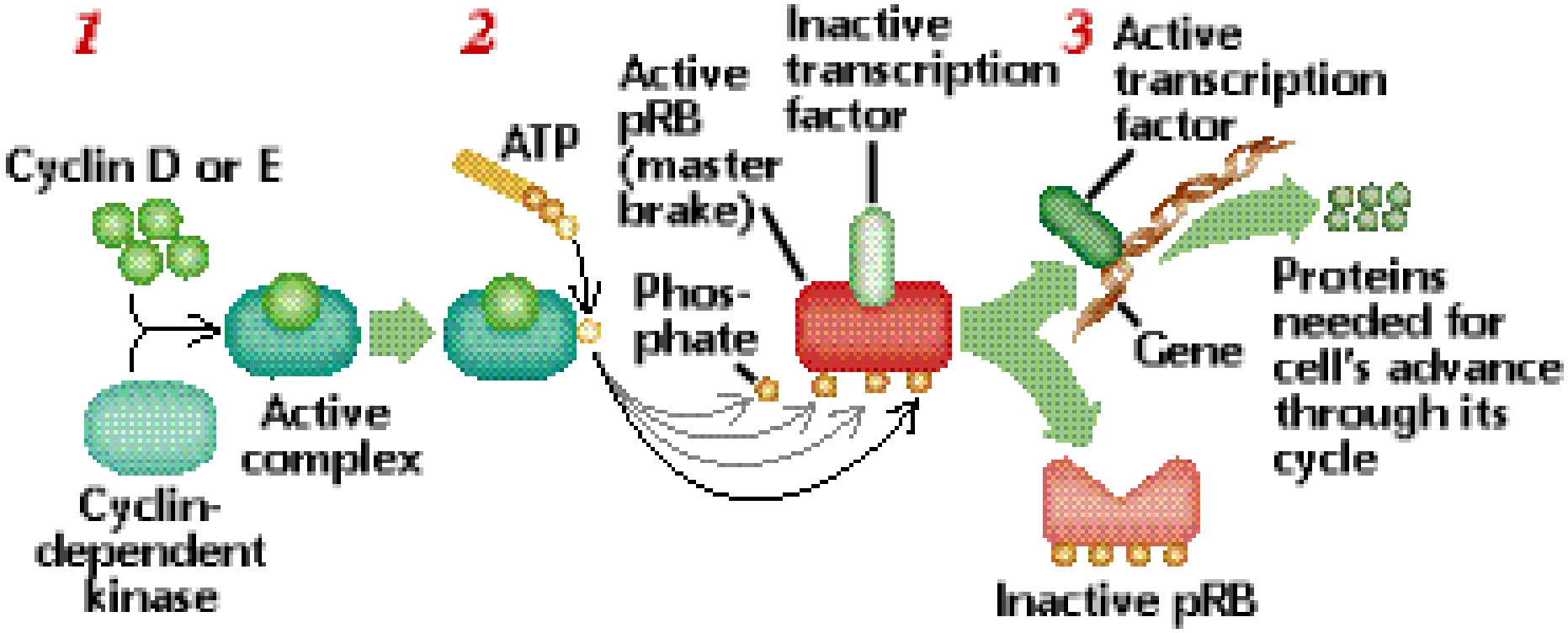
External Controls?

Many different stimuli exert G1 checkpoint control including DNA damage, contact inhibition and growth factor withdrawal.

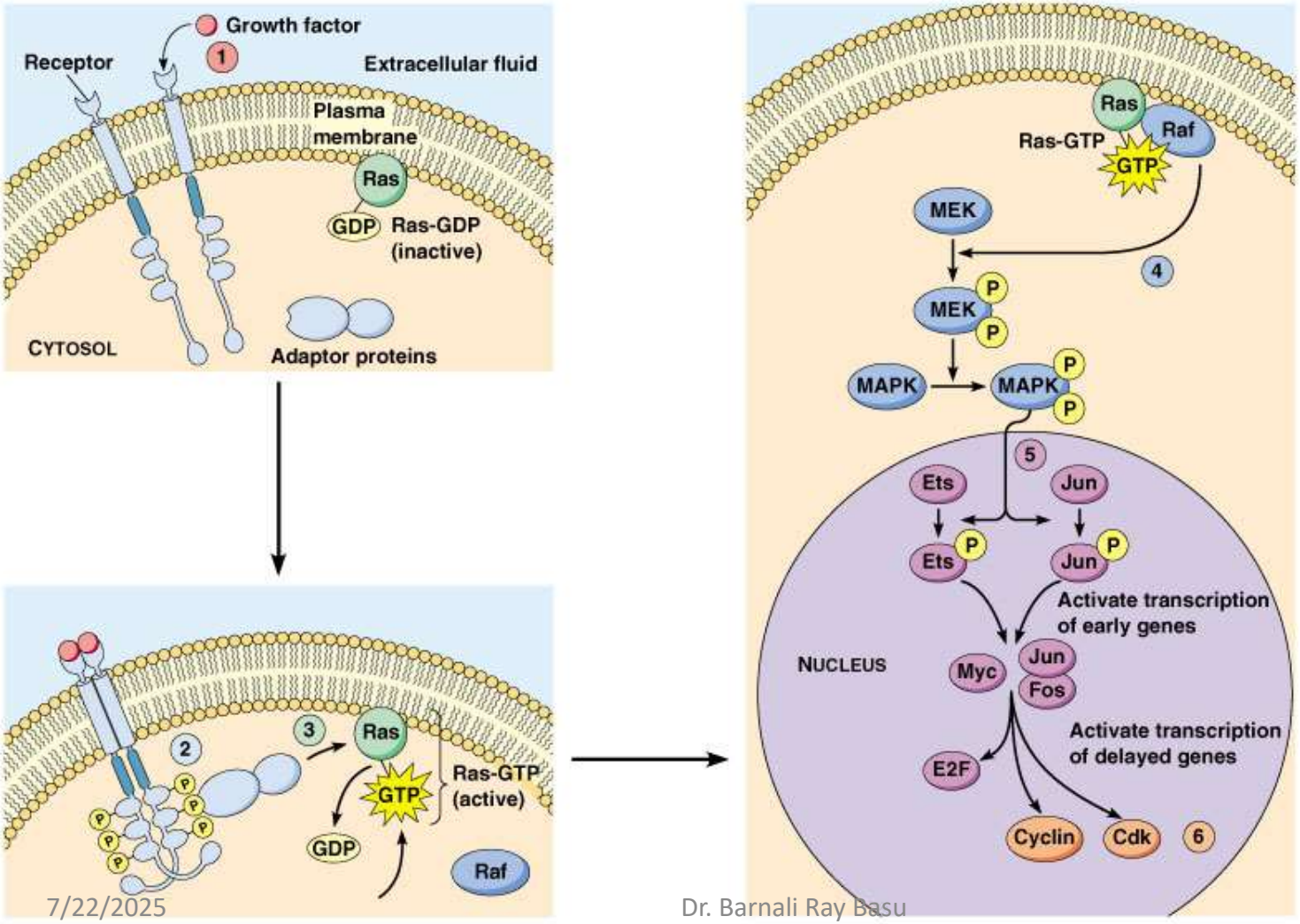
They act to inhibit kinases (in a mechanism similar to Jacob Monod).

Growth factors, promoting cell division, stimulate transcription of Cyclins

FLICKING THE SWITCH ON



Growth Factor Signaling Through the Ras Pathway → crossing of G1 checkpoint



Ras*, Raf*

↓

MAPK cascade

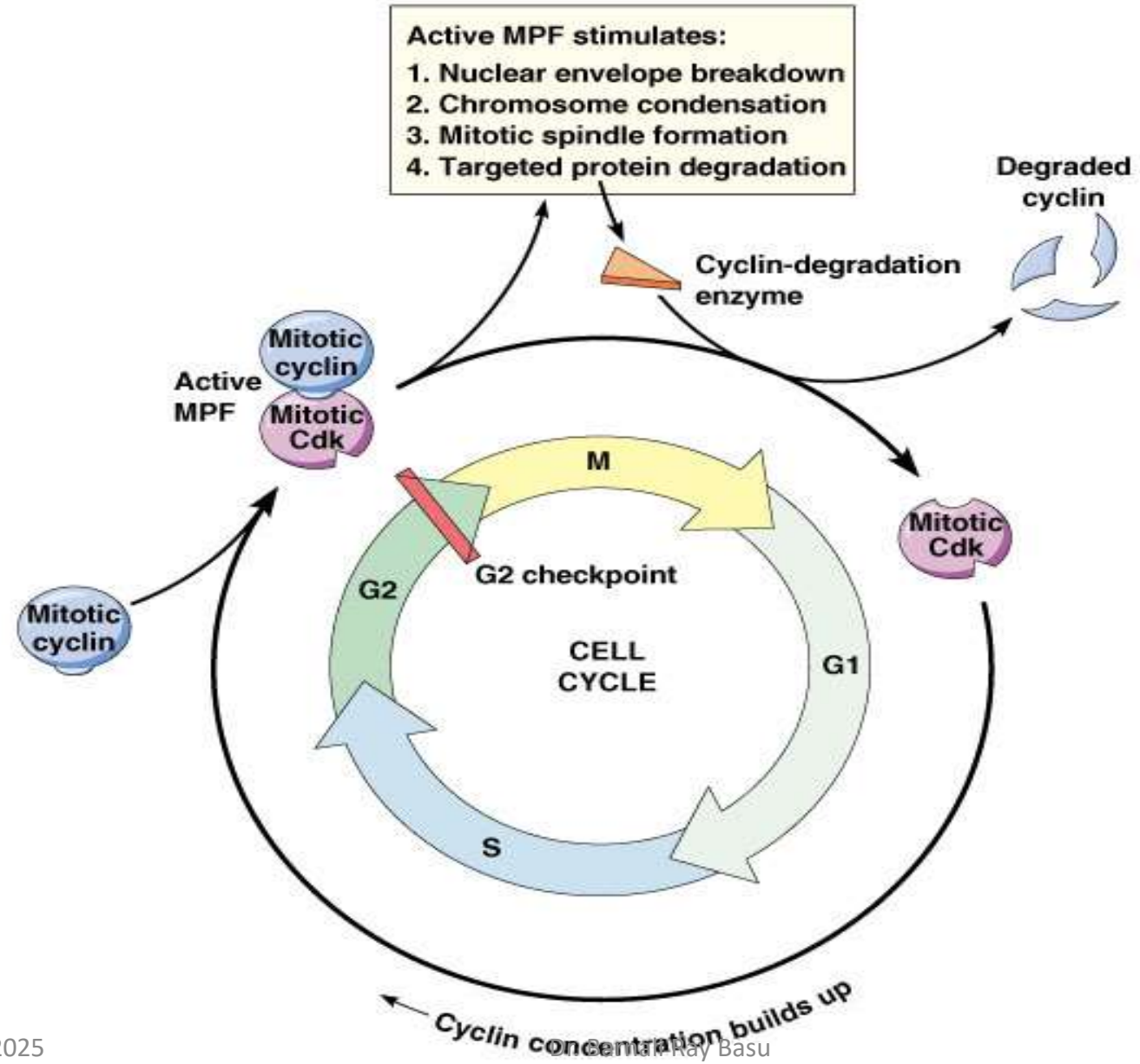
↓

Activation of nuclear TFs

↓

Activation of G1 Cdk cyclin genes: G1 → S

G2 checkpoint



G2/M DNA damage checkpoint

The **G2/M DNA damage checkpoint** prevents the cell from entering mitosis (M phase) if the genome is damaged.

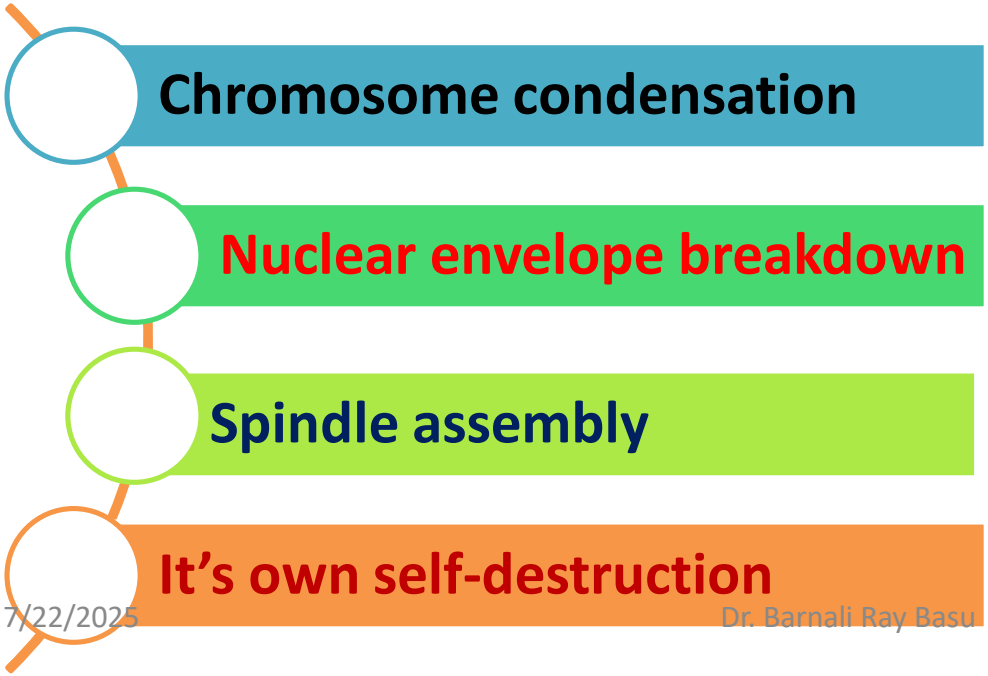
It also checks if the cell is big enough (i.e. has the resources to undergo mitosis)

Almost exclusively, internally controlled

Kinases – add a phosphate group (phosphorylate)

G2 Checkpoint Control by MPF

- Active MPF = Mitotic Cdk + mitotic cyclin
- Cdk is cyclin-dependant kinase
- MPF controls G2 → M by phosphorylating and activating proteins involving in:



M checkpoint

The M checkpoint is where the attachment of the spindle fibres to the centromeres is assessed.

Only if this is correct can mitosis proceed.

Failure to attach spindle fibres correctly would lead to failure to separate chromosomes

Kinases – add a phosphate group (phosphorylate)

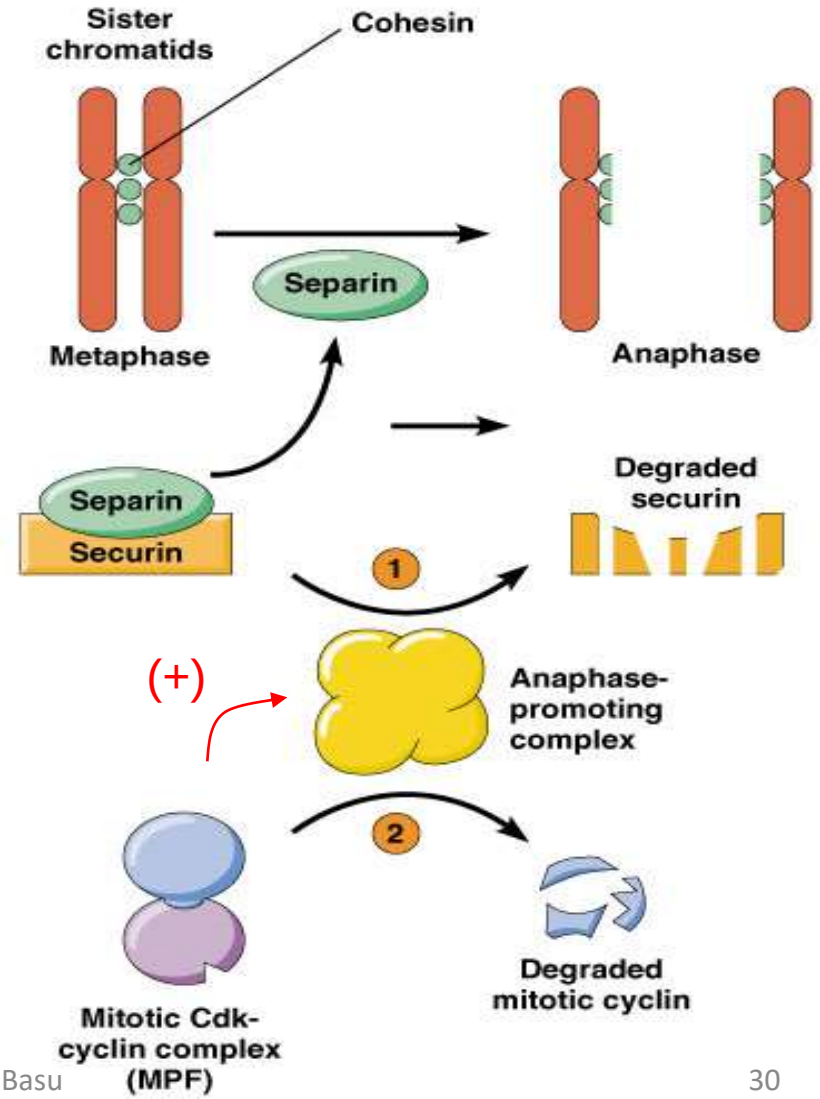
MPF may:

- phosphorylate histone protein H1 to condense chromatin.
- phosphorylate nuclear lamins to break nuclear envelope.
- phosphorylate MAPs (microtubule-associated proteins) resulting in the formation of spindle

Spindle Assembly Checkpoint Controls Metaphase → Anaphase

- MPF (+) anaphase promoting complex, which destroys:
  1. Securin, which allows separin protease to cleave cohesin.
  2. Mitotic cyclin, which causes loss of MPF activity, leading to chromosome decondensation and envelope reformation.

- Mad2 signal stops coming from kinetochore MT's once attached, also **(+) APC.**



- The Cell Cycle Is Regulated by **Protein Kinases**.
- The mechanism regulating the progression of cells through their division cycle is highly conserved in evolution, and plants have retained the basic components of this mechanism.
- The key enzymes that control the transitions between the different states of the cell cycle, and the entry of nondividing cells into the cell cycle, are the **cyclin-dependent protein kinases, or CDKs**

- Cell division is a vital process that requires orderly progression .
- Endogenous hormones such **as auxin,cytokinins, abscisic acid, gibberellins and brassinosteroids** as well as environmental factors all regulate progression through the cell cycle.
- cell cycle events take place with clock-like precision . Recent studies have demonstrated that cell cycles in plants and animals are regulated by similar mechanisms.
- A group of highly conserved serine/threonine kinases called **cyclin-dependent kinases(CDKs)** has been found to play a key role in guiding the cell cycle process.

Four classes of cyclins :

1. G1-cyclins — help to promote passage through " Start" or the restriction point in late G1

2. G1/S-cyclins — bind Cdks at the end of G1 and commit the cell to DNA replication

3. S-cyclins – binds Cdks during S phase and are required for the initiation of DNA replication

4. M-cyclins — promote the events of mitosis

- **Protein kinases** are enzymes that phosphorylate proteins using ATP.

- The regulated activity of CDKs is essential for the transitions from G1 to S and from G2 to M, and for the entry of nondividing cells into the cell cycle.
- The transition from G1 to S requires a set of cyclins (G1 cyclins) different from those required in the transition from G2 to mitosis, where mitotic cyclins activate the CDKs .
- CDKs possess two tyrosine phosphorylation sites: One causes activation of the enzyme; the other causes inactivation.
- Specific kinases carry out both the stimulatory and the inhibitory phosphorylation

- Similarly, **protein phosphatases** can remove phosphate from CDKs, either stimulating or inhibiting their activity, depending on the position of the phosphate.

- The addition or removal of phosphate groups from CDKs is highly regulated and an important mechanism for the control of cell cycle progression .

- Cyclin inhibitors play an important role in regulating the cell cycle in animals, and probably in plants as well, although little is known about plant cyclin inhibitors.

CDK activity can be regulated in various ways, but two of the most important mechanisms are

(1) cyclin synthesis and destruction and

(2) the phosphorylation and dephosphorylation of key amino acid residues within the CDK protein.

- CDKs are inactive unless they are associated with a cyclin. Most cyclins turn over rapidly.
- They are synthesized and then actively degraded (using ATP) at specific points in the cell cycle.
- Cyclins are degraded in the cytosol by a large proteolytic complex called the **proteasome**.
- Before being degraded by the proteasome, the cyclins are marked for destruction by the attachment of a small protein called **ubiquitin**, a process that requires ATP.

Summary: Cell Cycle Control

- A “clock” is running within the cell - of synthesis and degradation of cyclins - which activate cyclin-dependant kinases (Cdk’s), which activate other proteins to cause checkpoint transitions.

- The “clock” is adjusted (cyclins and Cdk’s are regulated) by other proteins, based on:
  - External signals (growth factors)
  - Internal signals (correct completion of previous step)

Summary of Controls:

- Three checkpoints,
  - G1 – assesses cell size, environment (contact inhibition)
  - G2 – assesses success of DNA replication
  - M – assesses have spindle fibres attached correctly to the chromosomes
- Mitosis promoting factor(MPF) - a protein (or number of proteins) which causes chromosomes to condense, nuclear membrane to disappear and so cells to enter mitosis