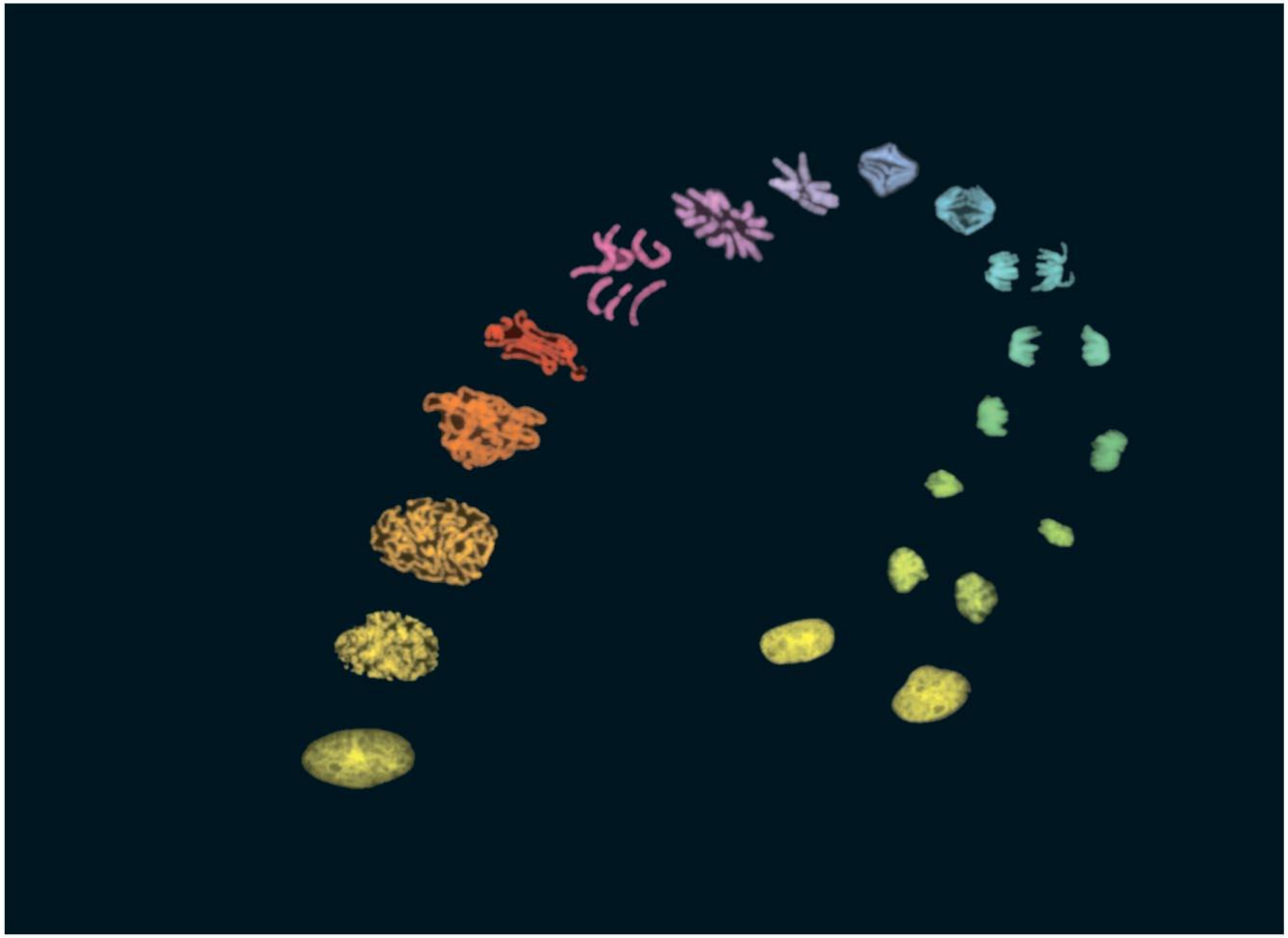
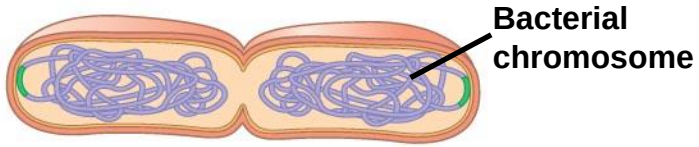
The Cell Cycle Control

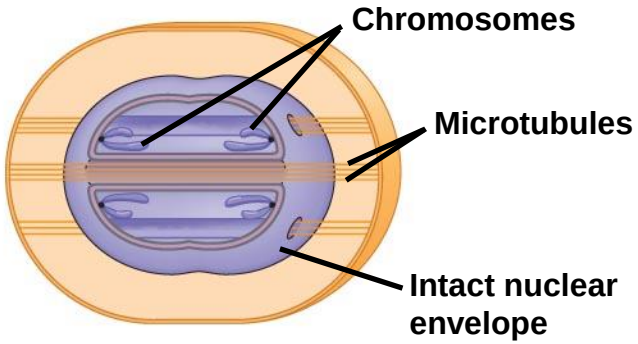


The Evolution of Mitosis

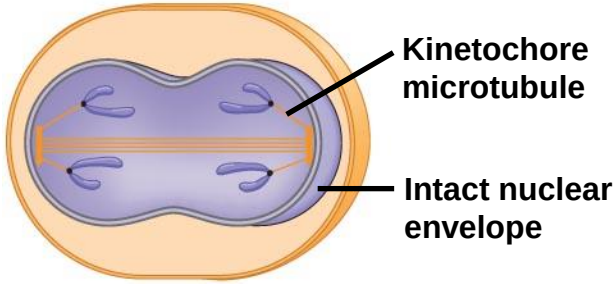
- Since prokaryotes evolved before eukaryotes, mitosis probably evolved from binary fission
- Certain protists exhibit types of cell division that seem intermediate between binary fission and mitosis



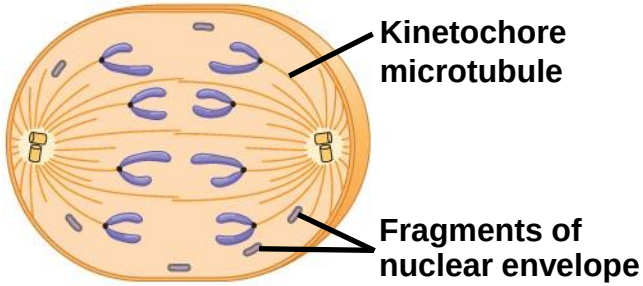
(a) Bacteria



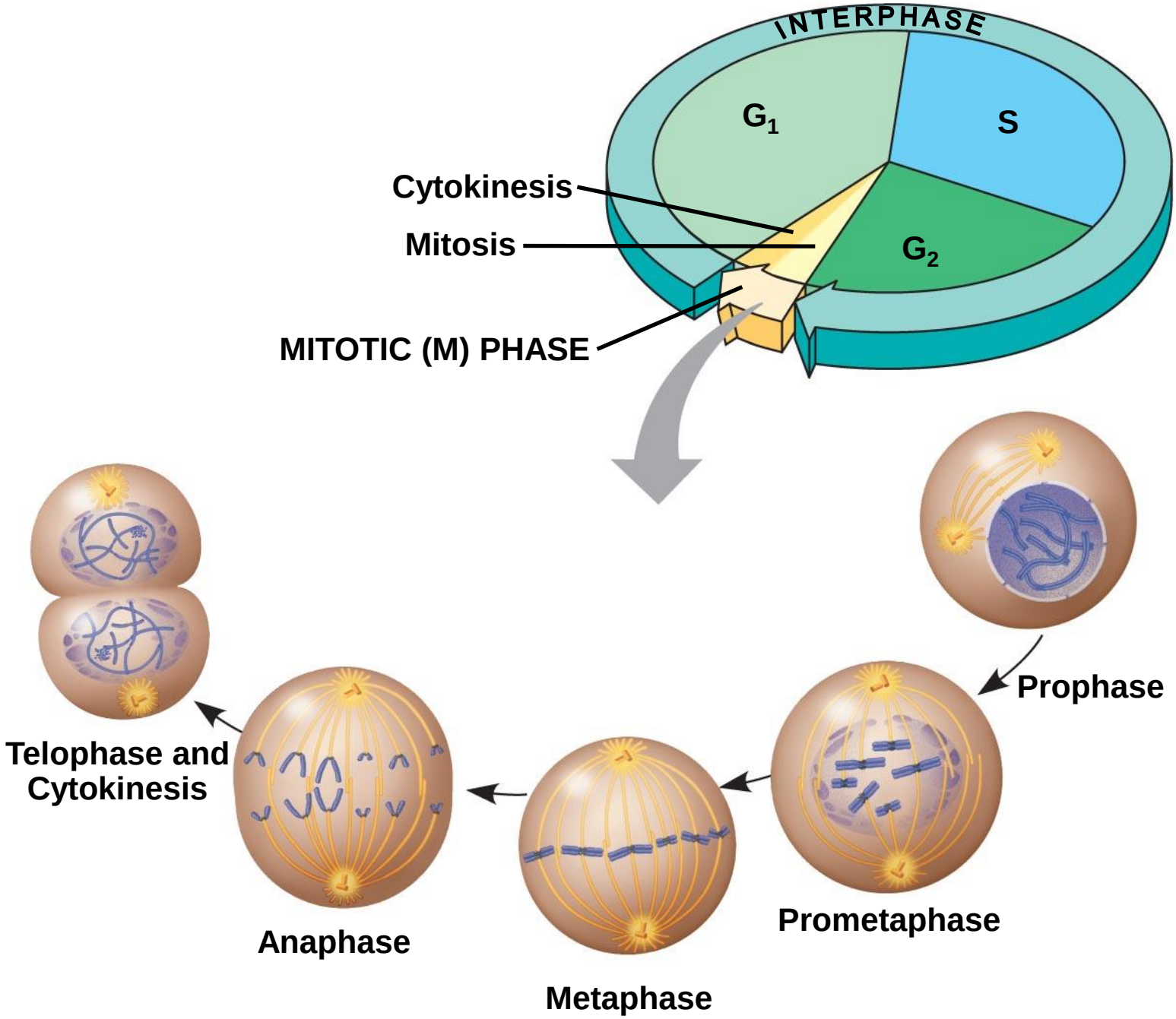
(b) Dinoflagellates



(c) Diatoms and yeasts



(d) Most eukaryotes



The eukaryotic cell cycle is regulated by a molecular control system

- The frequency of cell division varies with the type of cell
- These cell cycle differences result from regulation at the molecular level

Evidence for Cytoplasmic Signals

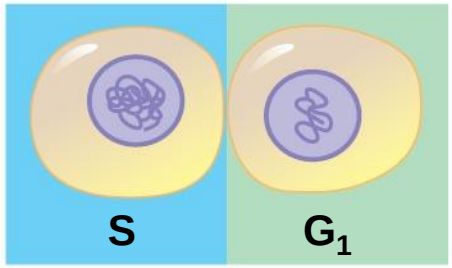
- The cell cycle appears to be driven by specific chemical signals present in the cytoplasm
- Some evidence for this hypothesis comes from experiments in which cultured mammalian cells at different phases of the cell cycle were fused to form a single cell with two nuclei

Masui and Markert's study of oocyte maturation led to the identification of **cyclin** and **cyclin-dependent kinase**

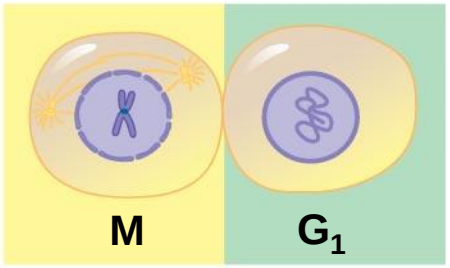
- Frog oocytes are dormant in G_2
- Progesterone makes oocytes progress to M
- Progesterone must be affecting triggers to progress to M
- 3 groups of donor oocytes
  - Progesterone for 2 hours
  - Progesterone for 12 hours
  - No progesterone
- Inject donor oocyte cytosol into recipient oocytes
- Only 12 hour donor caused progression
- Maturation Promoting Factor (MPF) is mitotic cyclin and cyclin-dependent kinase

EXPERIMENT

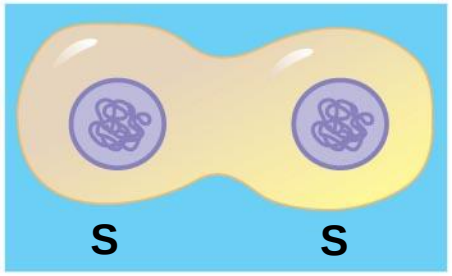
Experiment 1

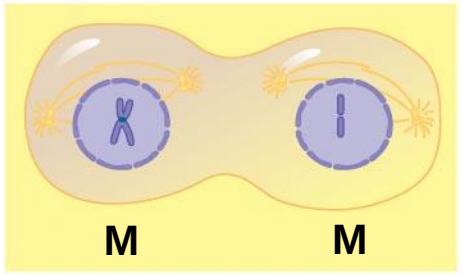


Experiment 2



RESULTS





When a cell in the S phase was fused with a cell in G_1, the G_1 nucleus immediately entered the S phase—DNA was synthesized.

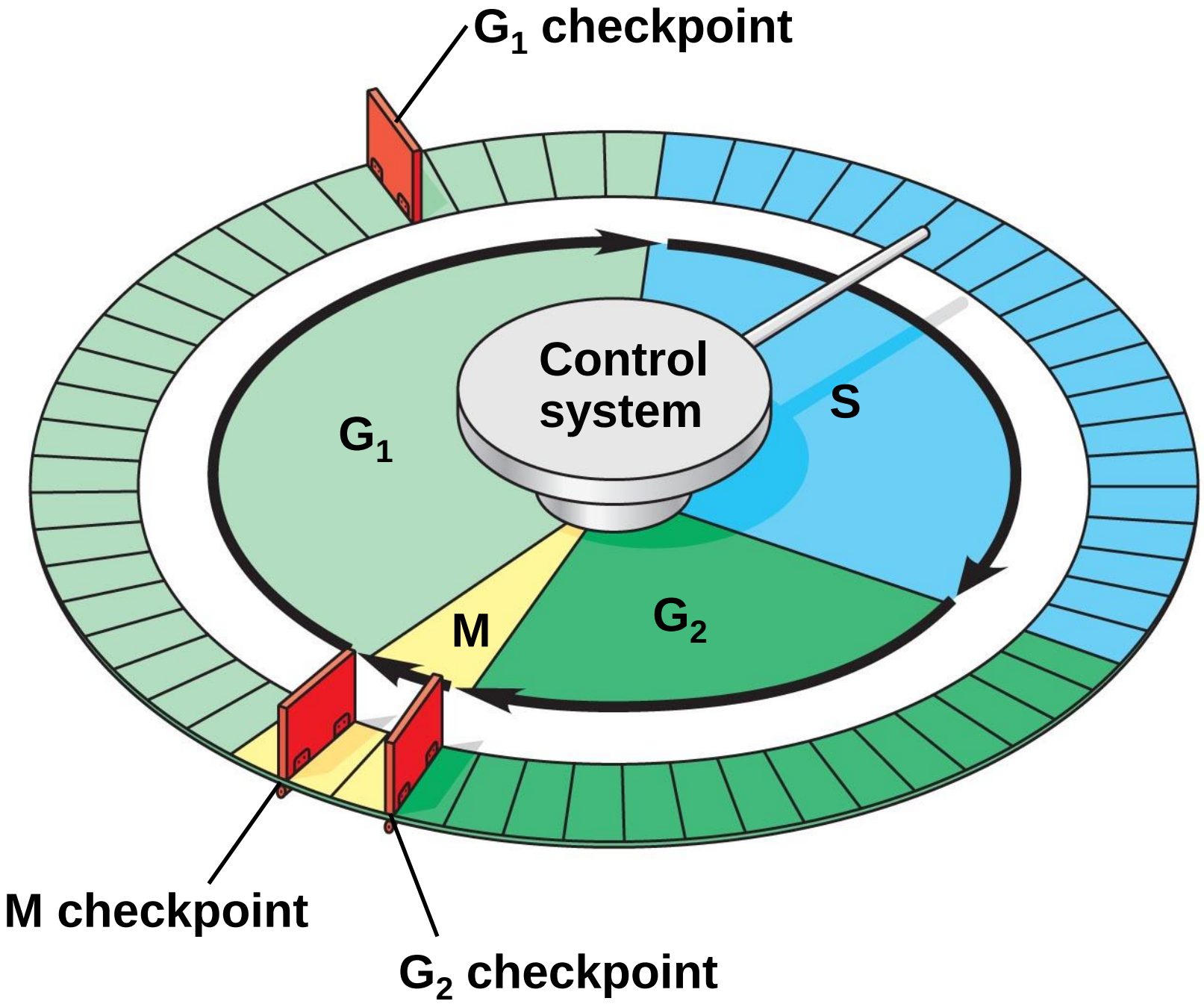
When a cell in the M phase was fused with a cell in G_1, the G_1 nucleus immediately began mitosis—a spindle formed and chromatin condensed, even though the chromosome had not been duplicated.

The Cell Cycle Control System

- The sequential events of the cell cycle are directed by a distinct **cell cycle control system**, which is similar to a clock

- The cell cycle control system is regulated by both **internal and external controls**

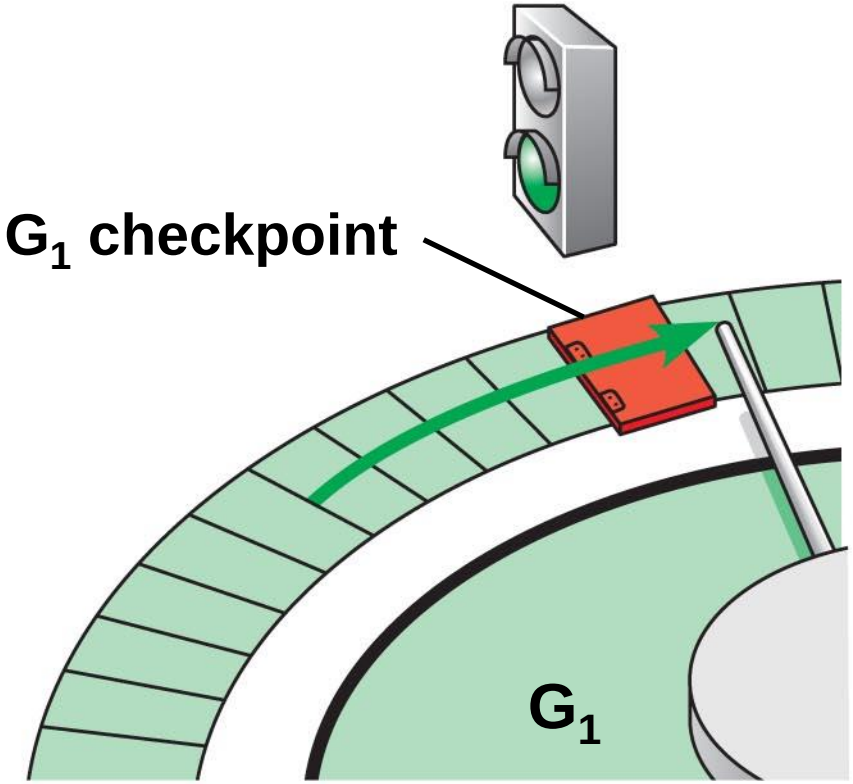
- The clock has specific **checkpoints** where the cell cycle stops until a go-ahead signal is received



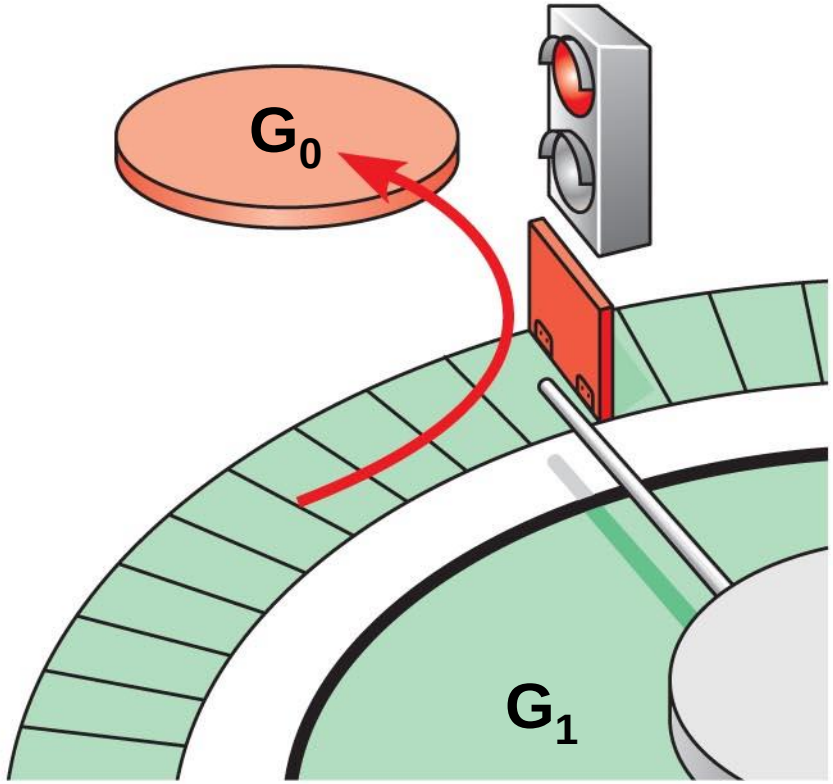
- For many cells, the G_1 checkpoint seems to be the most important one

- If a cell receives a go-ahead signal at the G_1 checkpoint, it will usually complete the S, G_2, and M phases and divide

- If the cell does not receive the go-ahead signal, it will exit the cycle, switching into a nondividing state called the **G_0 phase**



(a) Cell receives a go-ahead signal



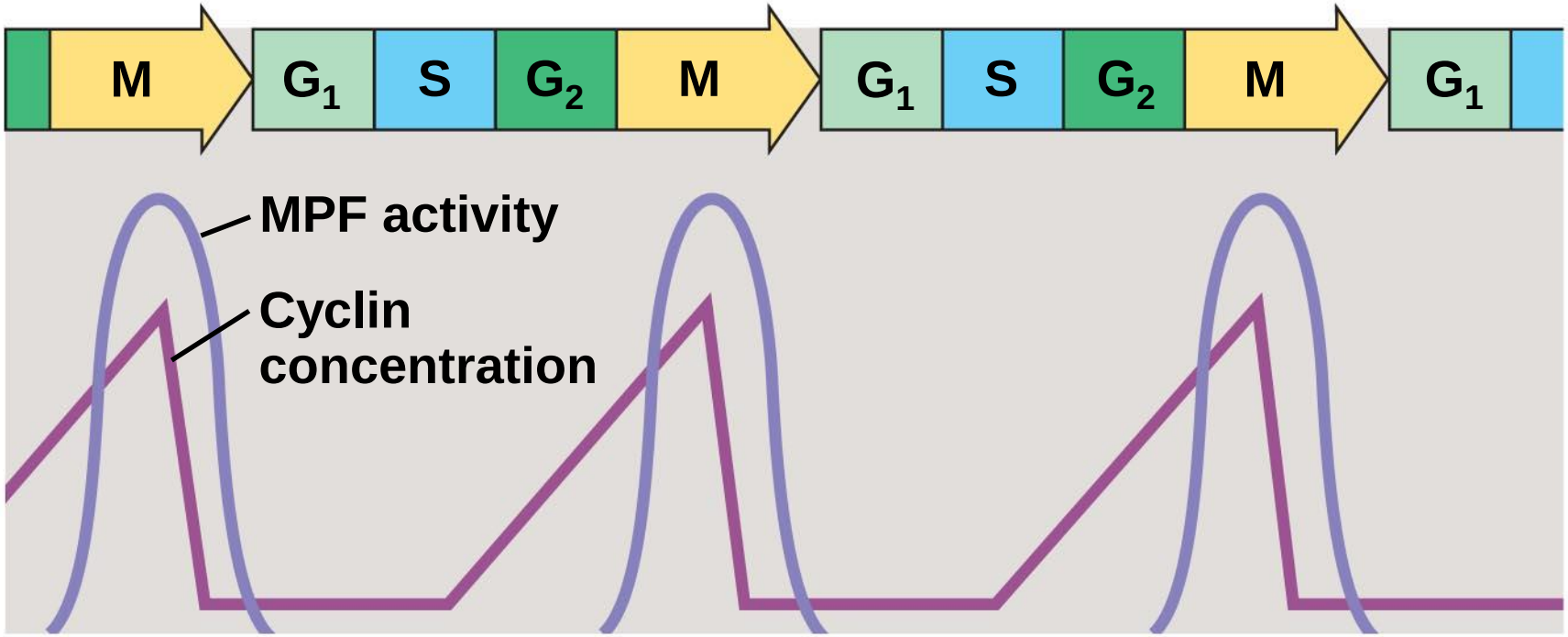
(b) Cell does not receive a go-ahead signal

The Cell Cycle Clock: Cyclins and Cyclin-Dependent Kinases

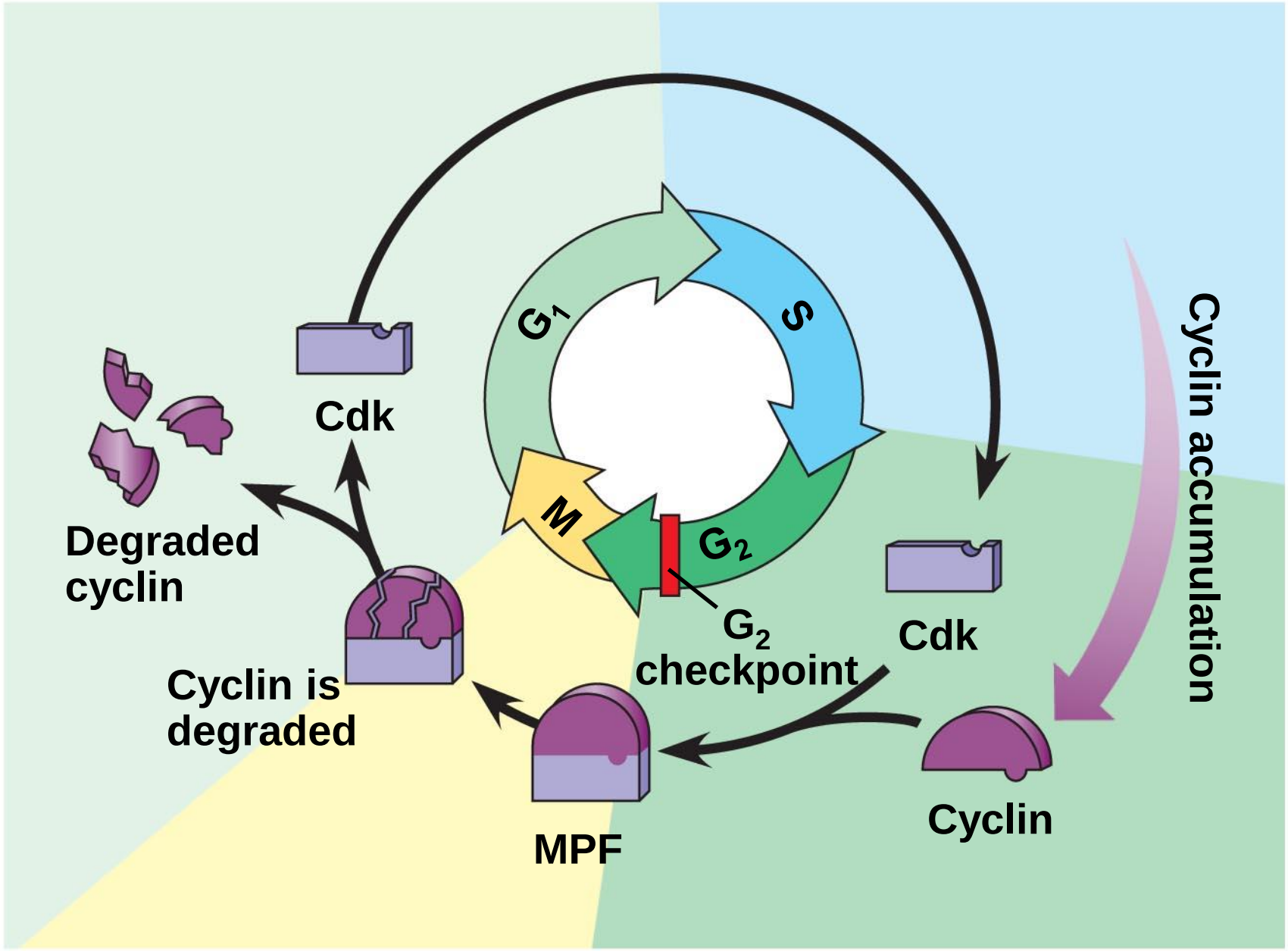
- Two types of regulatory proteins are involved in cell cycle control: **cyclins** and **cyclin-dependent kinases (Cdks)**

- The activity of cyclins and Cdks fluctuates during the cell cycle

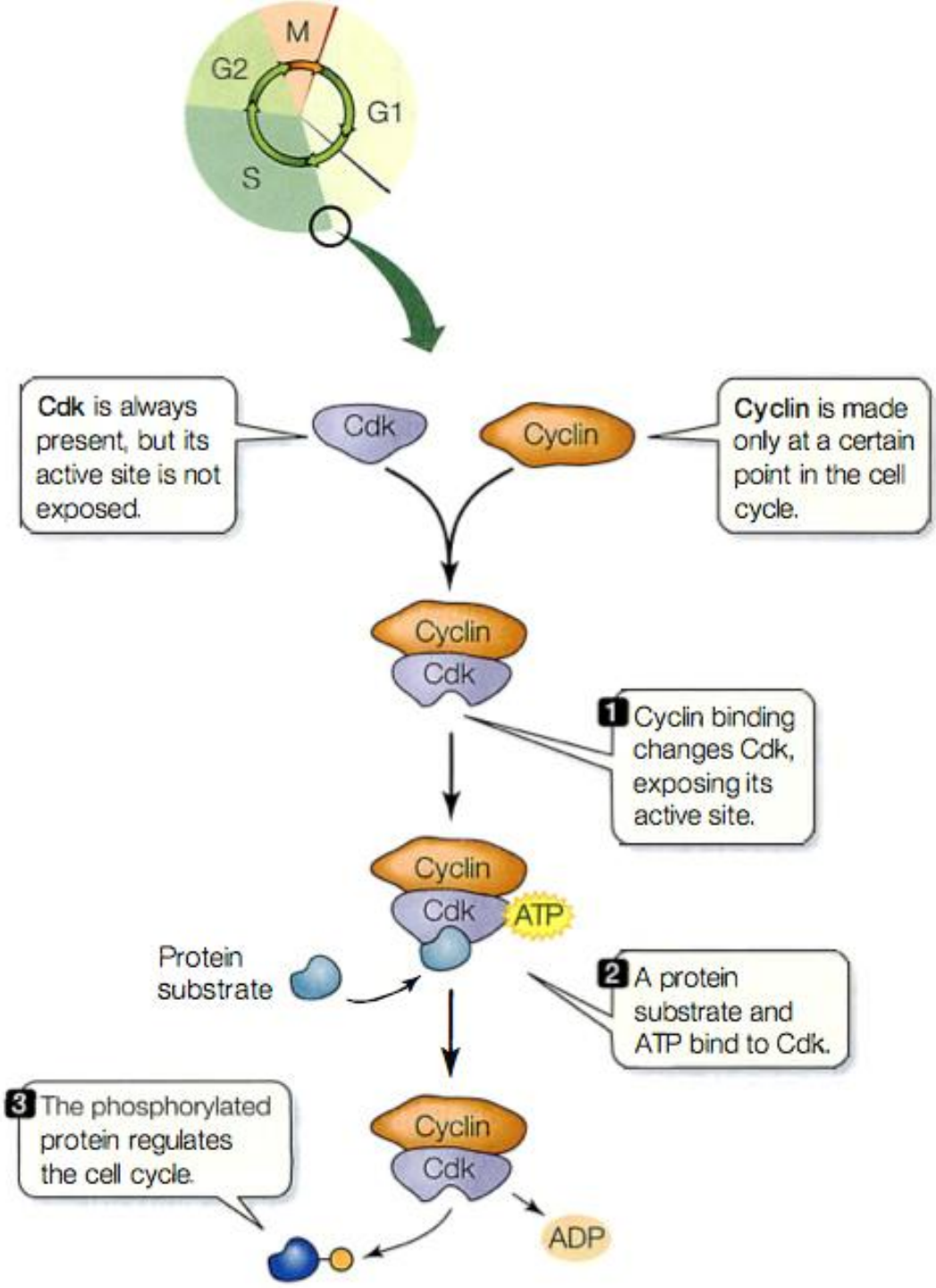
- **MPF** (maturation-promoting factor) is a cyclin-Cdk complex that triggers a cell's passage past the G_2 checkpoint into the M phase



(a) Fluctuation of MPF activity and cyclin concentration during the cell cycle



(b) Molecular mechanisms that help regulate the cell cycle


M
G2
G1
S
Cdk is always present, but its active site is not exposed.
Cdk
Cyclin
Cyclin is made only at a certain point in the cell cycle.
Cyclin
Cdk
1 Cyclin binding changes Cdk, exposing its active site.
Cyclin
Cdk
ATP
Protein substrate
2 A protein substrate and ATP bind to Cdk.
3 The phosphorylated protein regulates the cell cycle.
Cyclin
Cdk
ADP

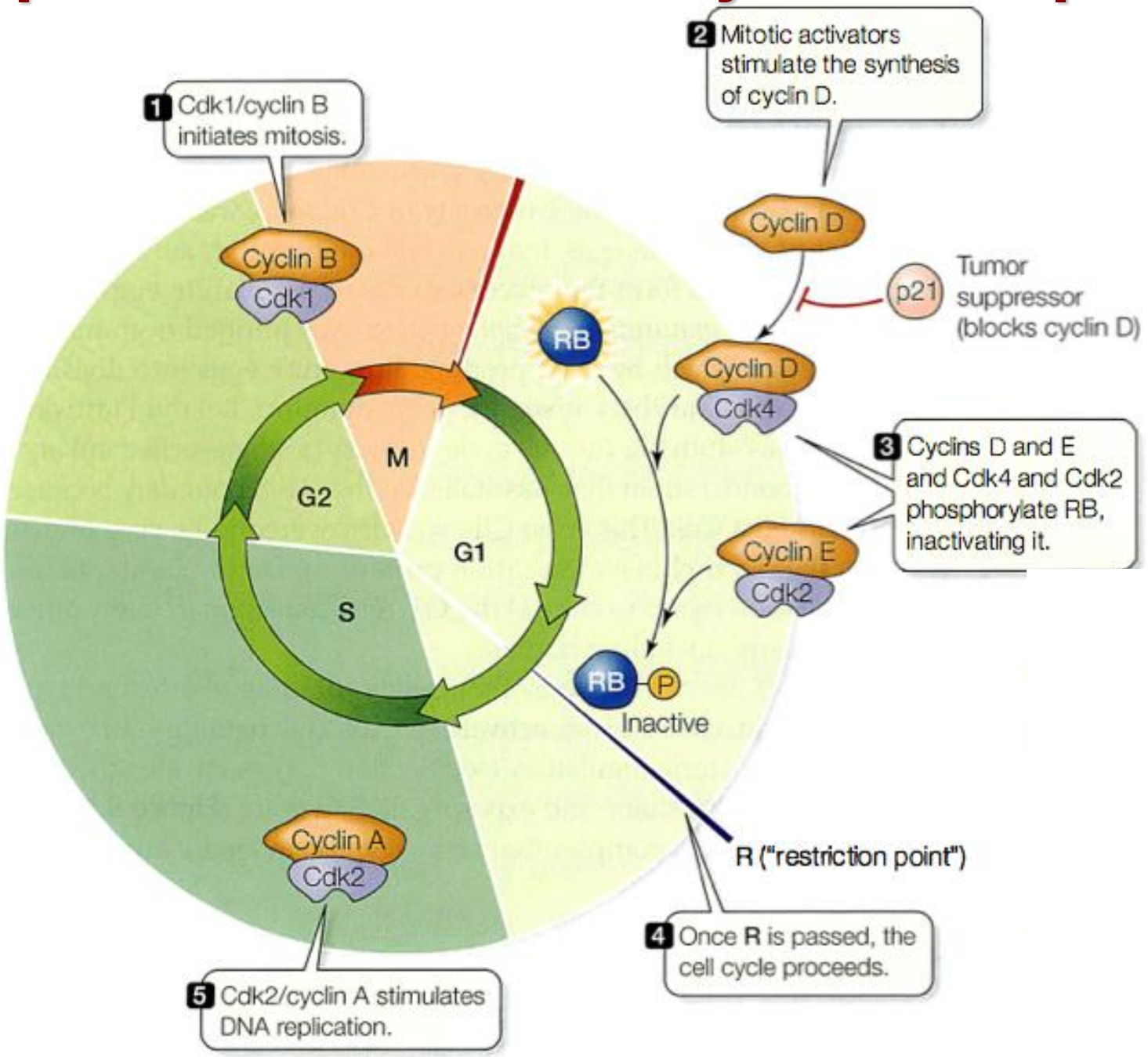
• **Cyclin D-Cdk4** acts during the middle of G1 . It moves the cell past the restriction point (R), a key decision point beyond which the rest of the cell cycle is normally inevitable.

• **Cyclin E-Cdk2** also acts in the middle of G1; it works in concert with Cyclin D-Cdk4 to move the cell cycle past the restriction point.

• **Cyclin A-Cdk2** acts during the S phase to stimulate DNA replication.

• **Cyclin B-Cdk1** acts at the G2-M boundary, initiating the transition to mitosis.

Rb protein: the first major checkpoint



pRB regulation depends on phosphorylation

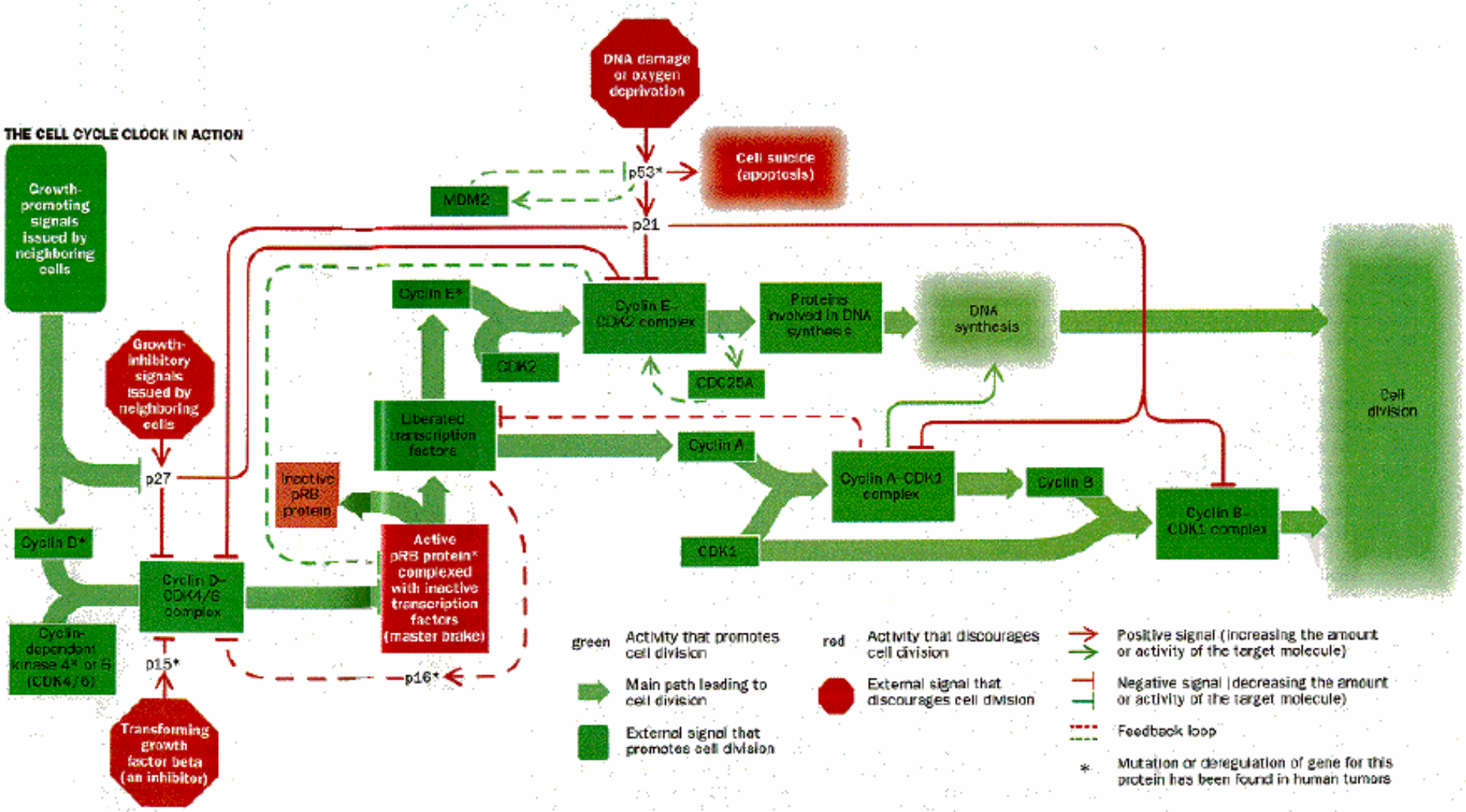
pRb binds to E2F transcription factors to block their function

pRb can actively inhibit cell cycle progression when it is dephosphorylated

Therefore phosphorylation inactivates its function.

At the end of mitosis (M phase) pRB depends on a phosphatase to dephosphyorylate it, allowing it to bind to E2F again

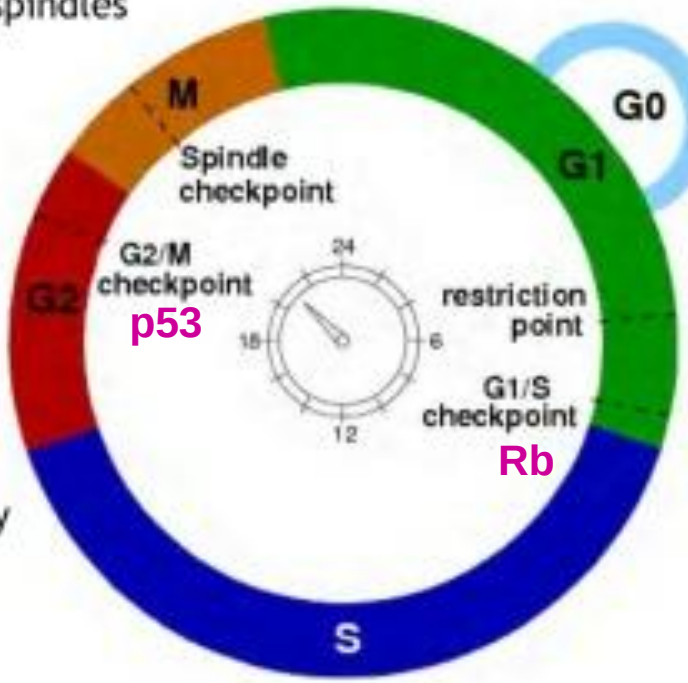
p53, p21 & The Second Major Checkpoint



Robert A. Weinberg, How Cancer Arises, *Scientific American 275*(3):62-70, September 1996.

M phase – In mitosis chromosomes drawn apart by molecular motors, cell divides. Many cancer drugs like taxol act here freezing the process and causing apoptosis. There is a checkpoint to ensure chromosomes are correctly attached to the spindles before segregation.

G1 is entered when the cell senses growth signals or mitogens. These start the process of cell division.



Cell crosses a restriction point c 8-10 hours into G1 - This is a point of no return: the cell is committed to divide or die.

G2/M - cell arranges and checks chromosomes. There is a major checkpoint here to ascertain that DNA replication has successfully occurred. If not, a normal cell undergoes apoptosis.

G1/S checkpoint –arrest here for cancer cells leads to apoptosis.

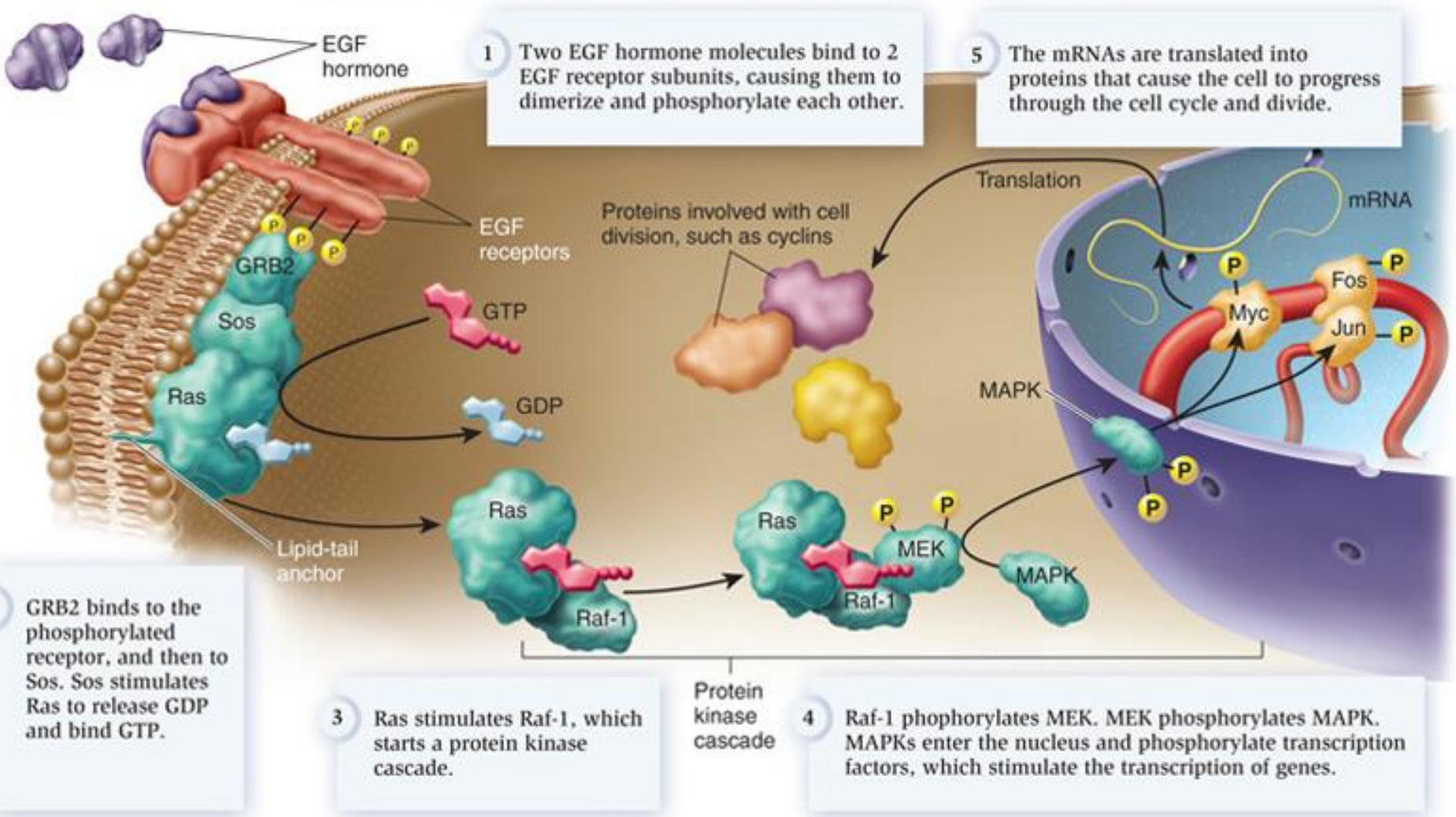
S phase - DNA is synthesised. Many cytotoxic anti-cancer drugs act here to disrupt DNA synthesis.

Cell Cycle Checkpoints

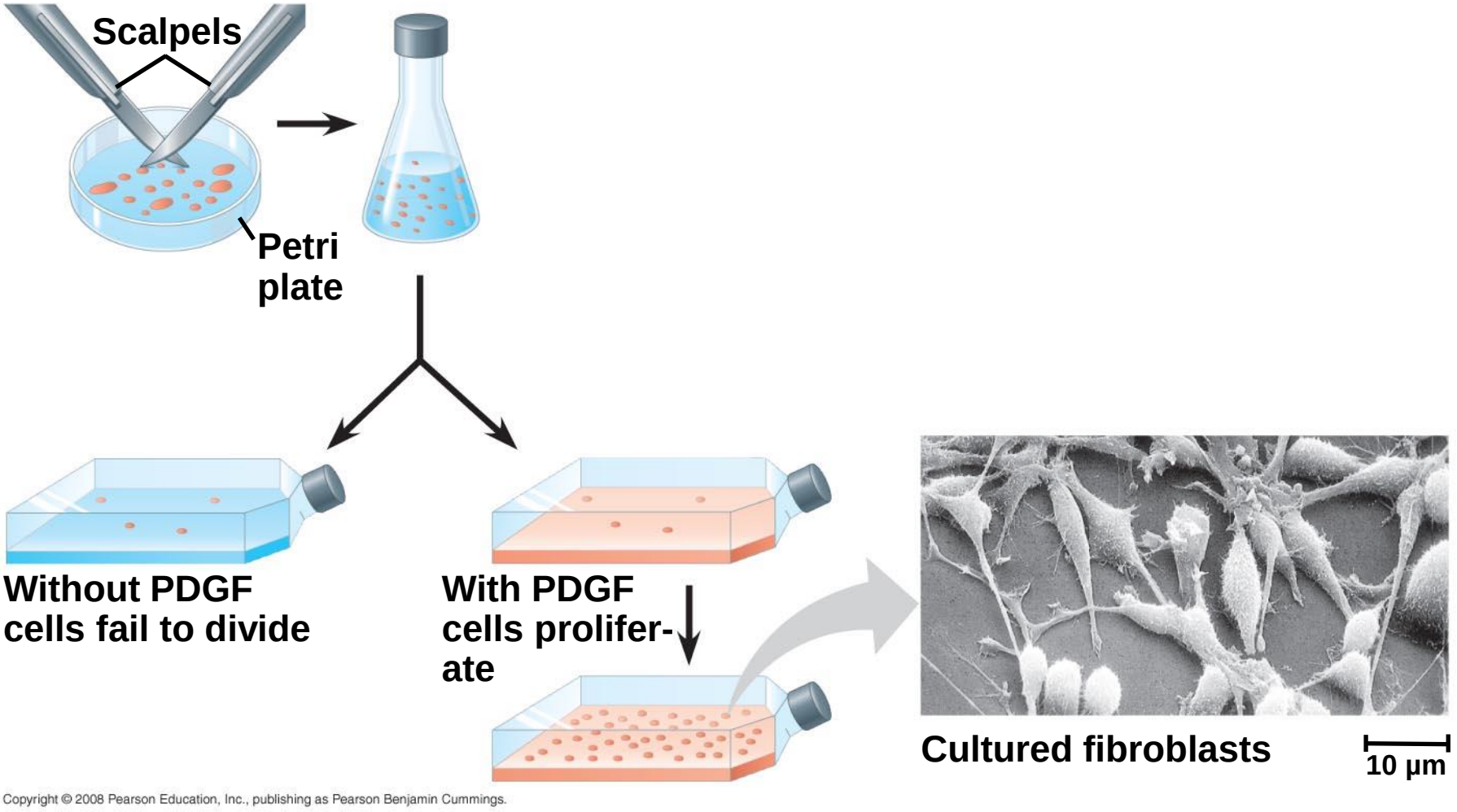
Stop and Go Signs: Internal and External Signals at the Checkpoints

- An example of an internal signal is that **kinetochores not attached to spindle** microtubules send a molecular signal that delays anaphase
- Some external signals are **growth factors**, proteins released by certain cells that stimulate other cells to divide
- For example, **platelet-derived growth factor** (PDGF) stimulates the division of human fibroblast cells in culture

External Signals-Growth Factors

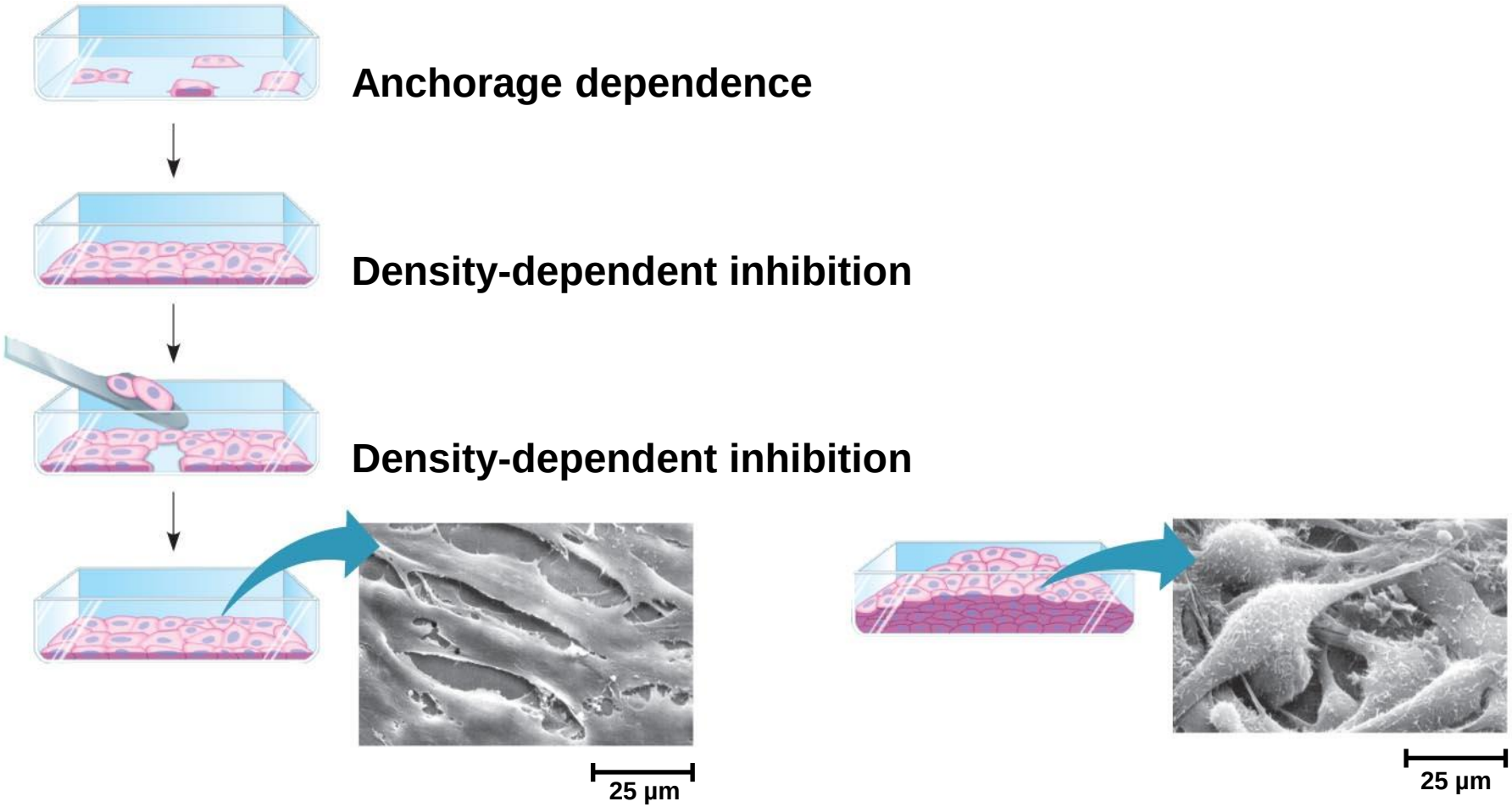


External Signals-Growth Factors



- Another example of external signals is **density-dependent inhibition**, in which crowded cells stop dividing
- Most animal cells also exhibit **anchorage dependence**, in which they must be attached to a substratum in order to divide

External Signals-Physical fctors



(a) Normal mammalian cells

(b) Cancer cells