Lecture 9:
The cell cycle

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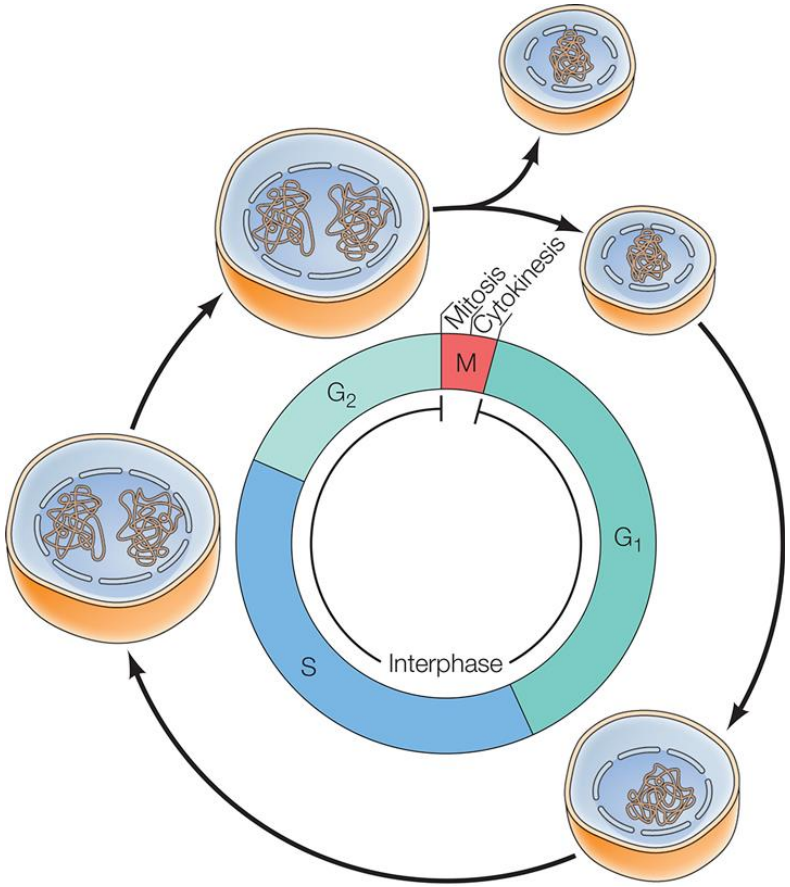
Some introduction

- Cells must divide for life to continue.
- Cell division involves DNA replication and separation of chromosomes (mitosis).
- A typical eukaryotic cell cycle divides ~every 24 hours.
  - Mitosis (nuclear division) and cytokinesis (cell division) = ~1 hour
- Yeast cells: 90 minutes

The cell cycle

- The cell cycle is divided into two basic stages:

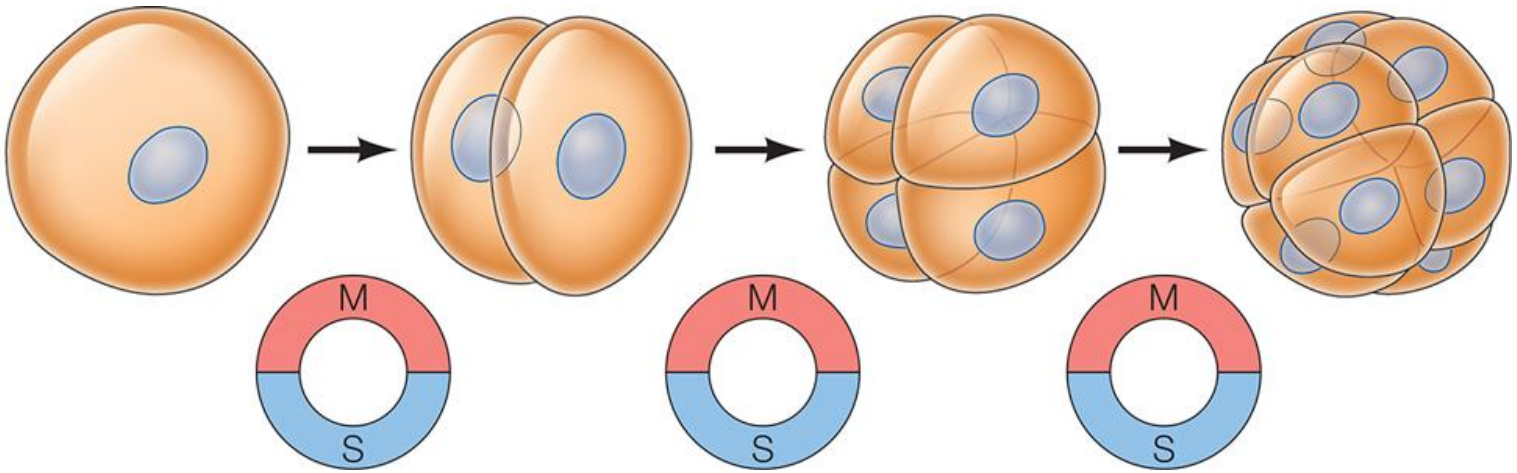
1. M phase: chromosomal segregation, nuclear and cell division
2. Interphase: cell growth and DNA replication occur in an orderly manner in preparation for cell division.
   - G1: increased metabolism and cell growth; cells are diploid (2n)
   - S: DNA replication; cells are 2-4n
   - G2: metabolism and cell growth; cells are 4n.

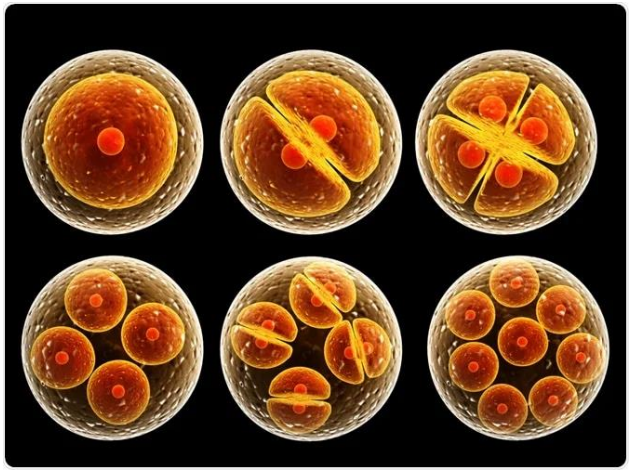


G = Gap

Special cases

- Zygote: no G1 or G2, but rapid S and M phases

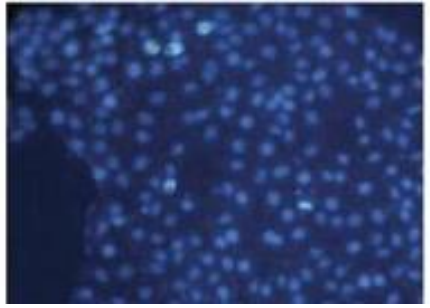


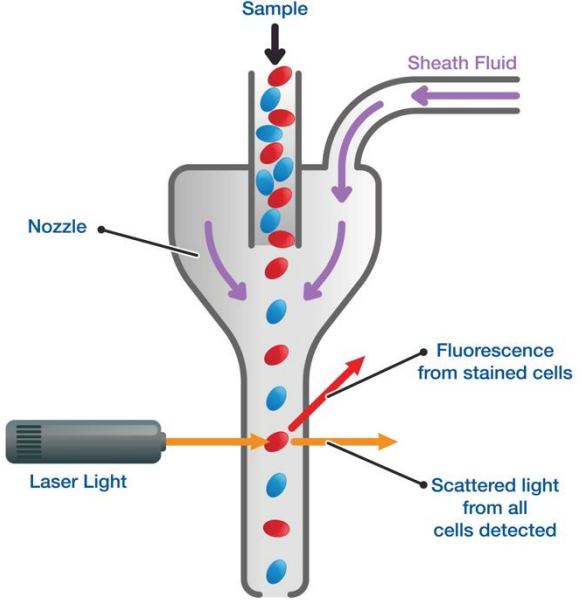


- Some cells (nerve cells) enter a quiescent stage (G_0 phase).
- Skin fibroblasts and cells of some internal organs divide as needed.
  - These cells are arrested in G_0 and can re-enter the cell cycle in the presence of appropriate extracellular signals.

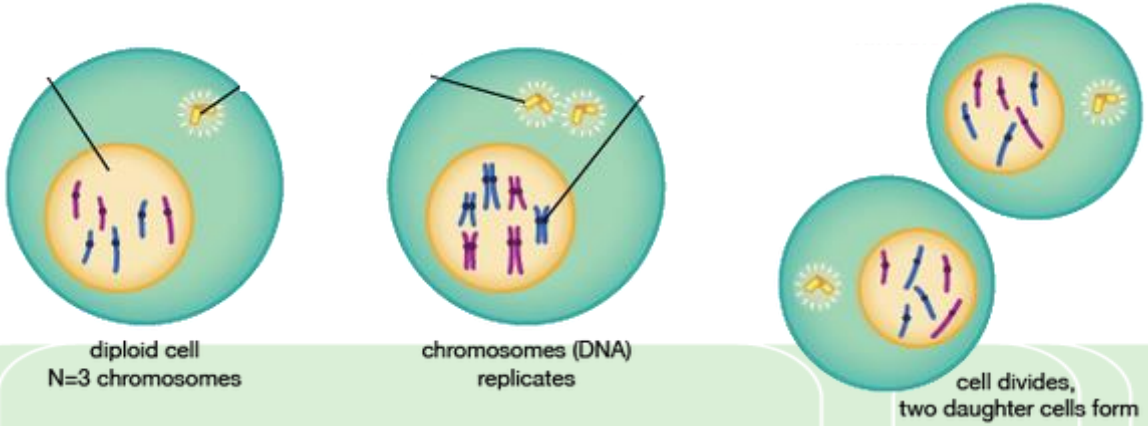
The use of flow cytometry

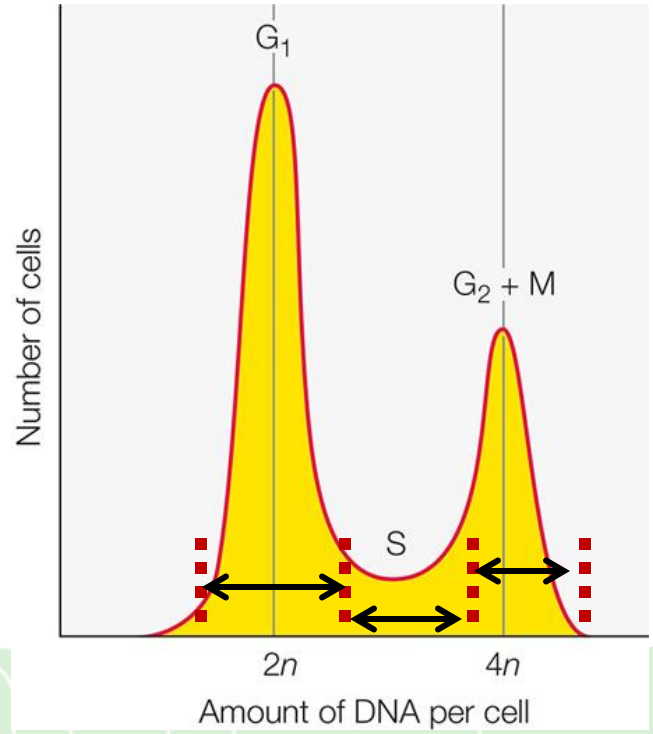
To distinguish dividing cells by the amount of their DNA content

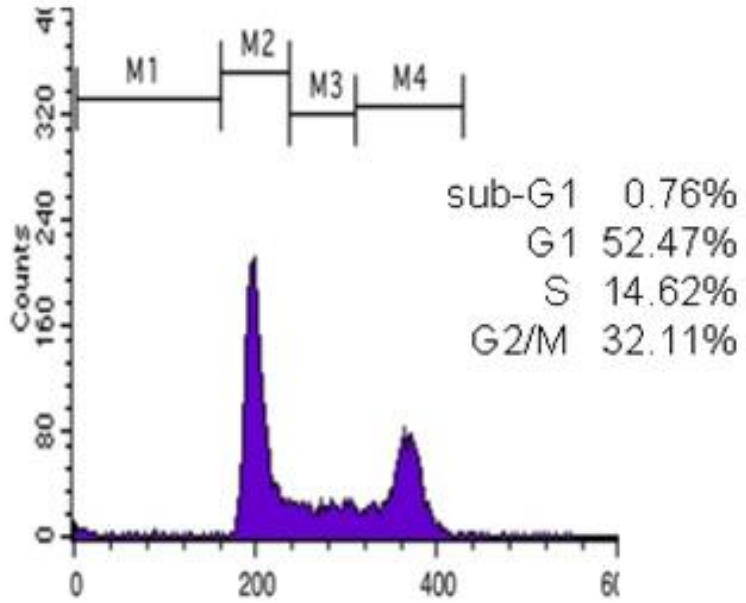




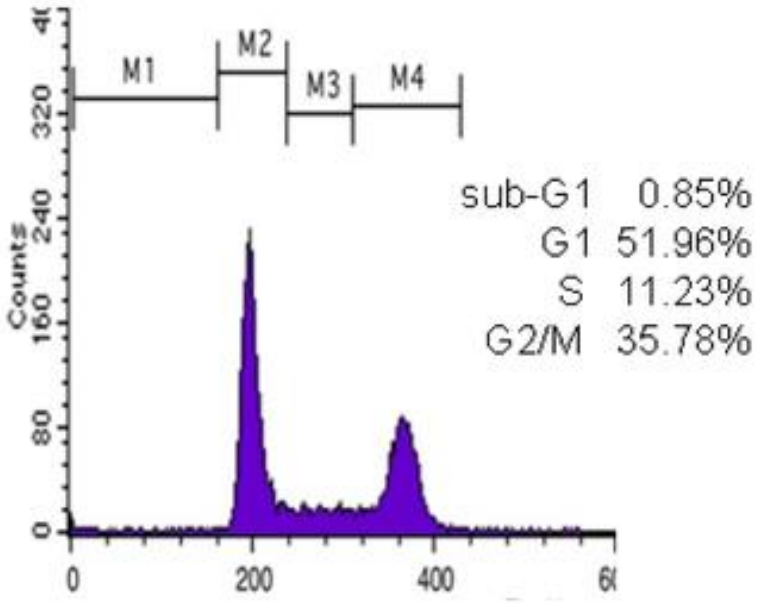
- DNA is stained and cells are analyzed by instruments known as flow cytometry or fluorescence-activated cell sorter (FACS).
- Cells in G1 are diploid (containing two copies of each chromosome) and referred to as 2n (n = haploid DNA content).
- At the end of the S phase and the beginning of the M phase, the DNA content is 4n.
- Cells in the S phase have DNA contents ranging from 2n to 4n.
- At the end of the M phase, DNA decreases 2n.



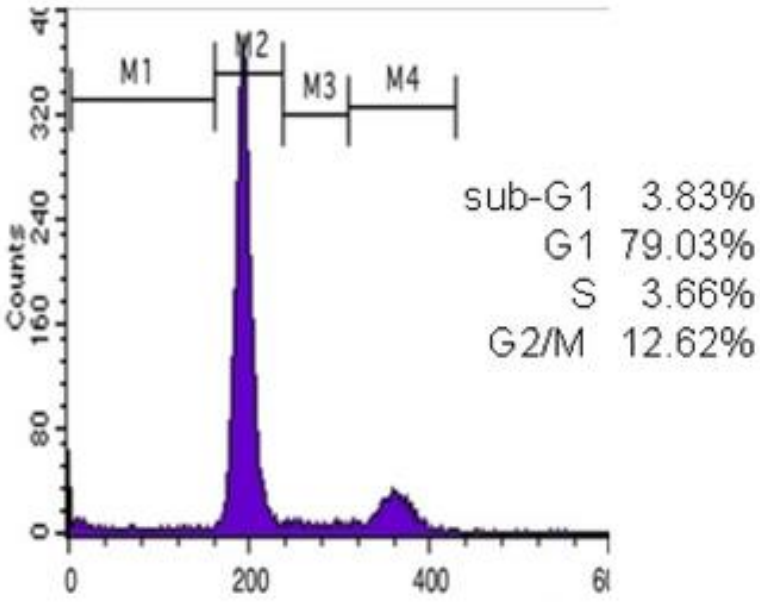




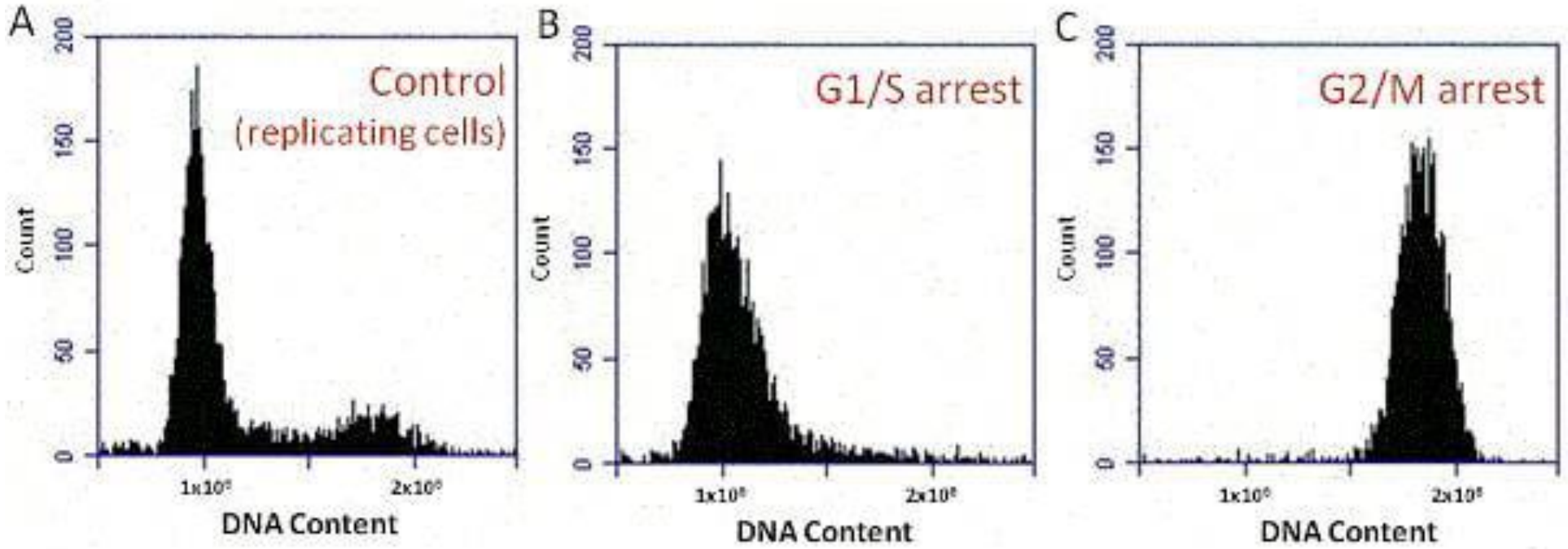
0 hr

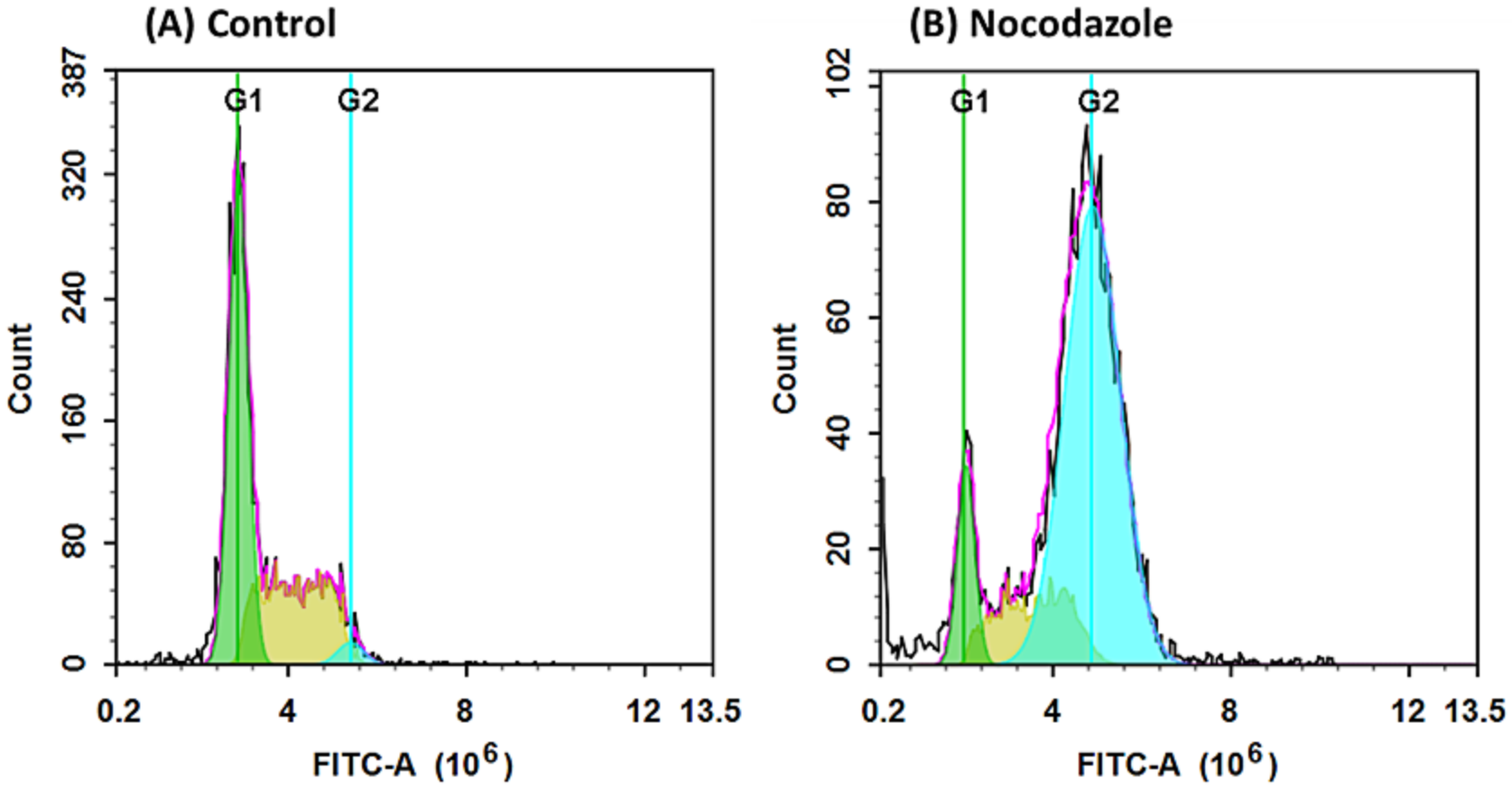


24 hr



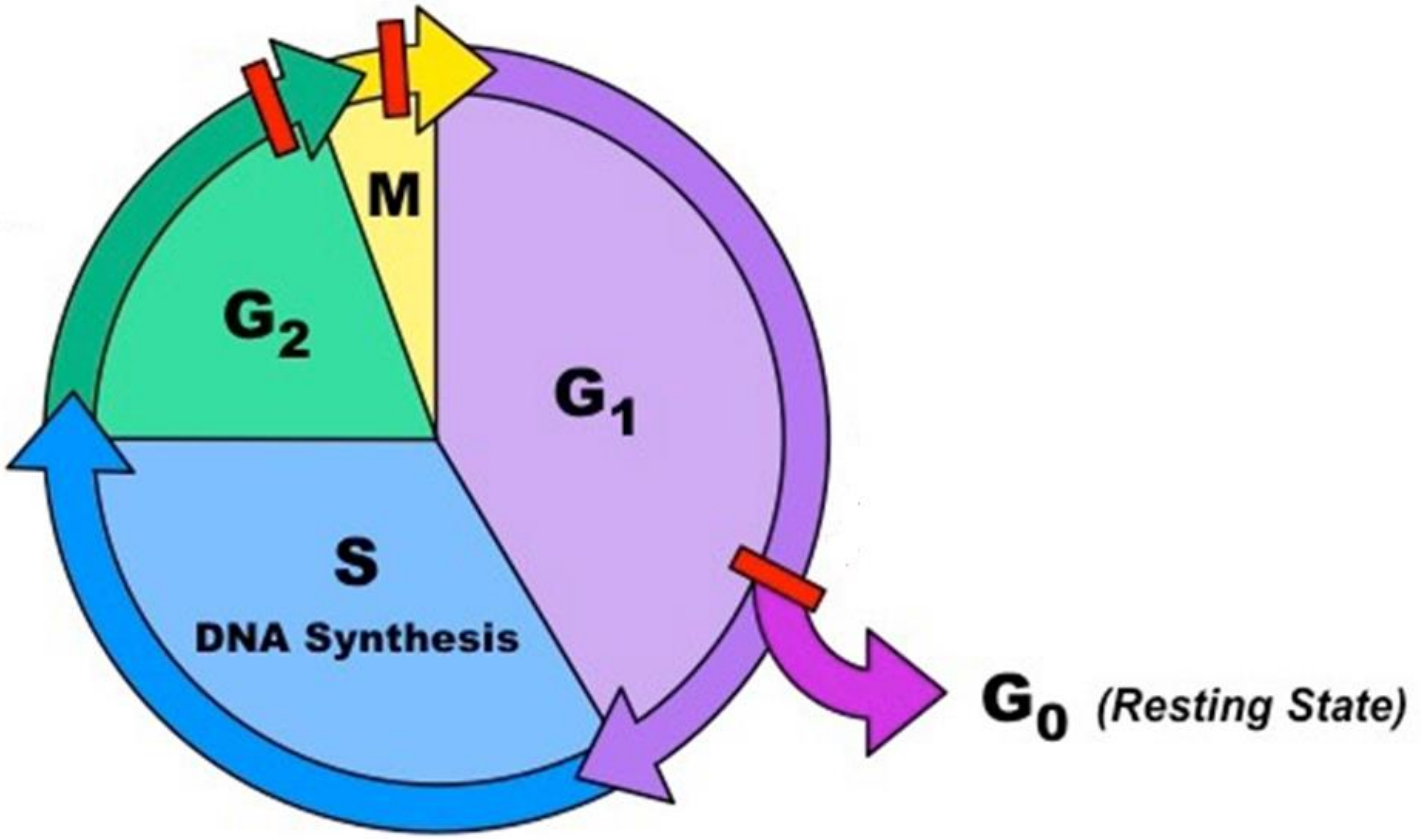
48 hr


A
Control
(replicating cells)
Count
0
50
100
150
200
1x10⁶
2x10⁶
DNA Content
B
G1/S arrest
Count
0
50
100
150
200
1x10⁶
2x10⁶
DNA Content
C
G2/M arrest
Count
0
50
100
150
200
1x10⁶
2x10⁶
DNA Content


(A) Control
G1
G2
Count
0
80
160
240
320
387
0.2
4
8
12
13.5
FITC-A (10^6)
(B) Nocodazole
G1
G2
Count
0
20
40
60
80
102
0.2
4
8
12
13.5
FITC-A (10^6)

Cell cycle checkpoints

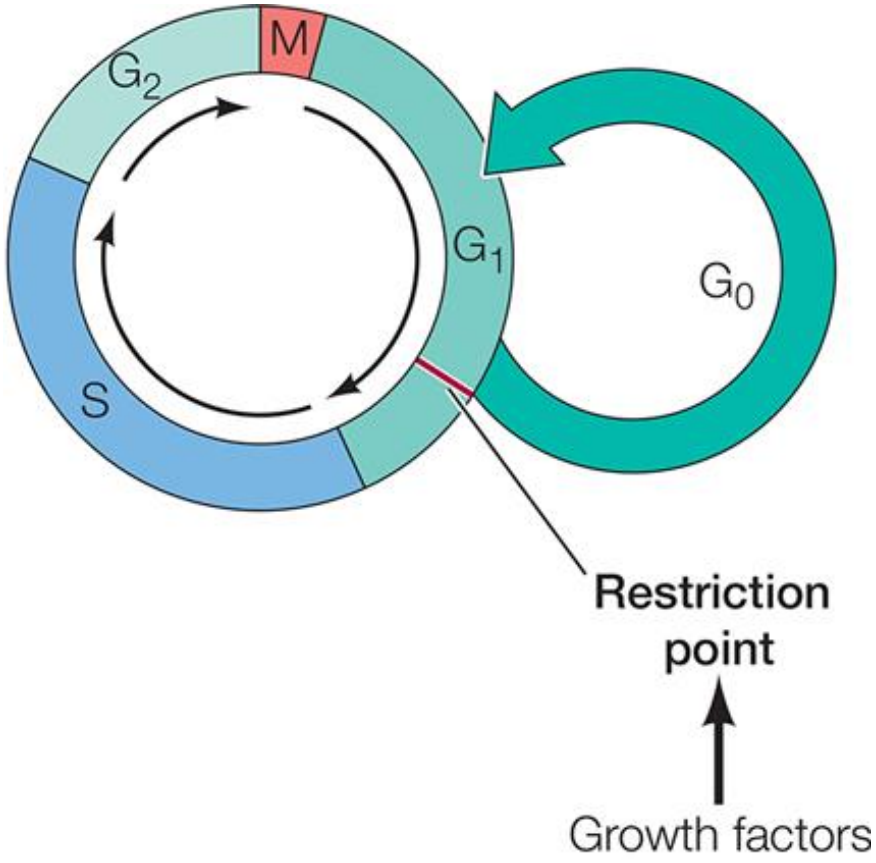
- Cells have several checkpoints to ensure that there are no mistakes before dividing.



Restriction point

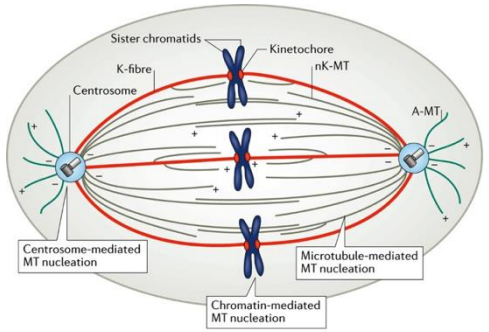
1. Restriction point: a decision point in late G1 is regulated by the extracellular growth factors

- If not there, cells enter G_0 phase where they are metabolically active without growth.
  - Skin fibroblasts are arrested in G_0 until they are stimulated to divide by the platelets' platelet-derived growth factor, which is released during clotting to repair damaged tissues.



Checkpoints

- Cells are arrested at G1, S, and G2 and do not proceed to the next phase unless DNA is error-free.
- Spindle assembly checkpoints monitor the alignment of chromosomes on the mitotic spindle.



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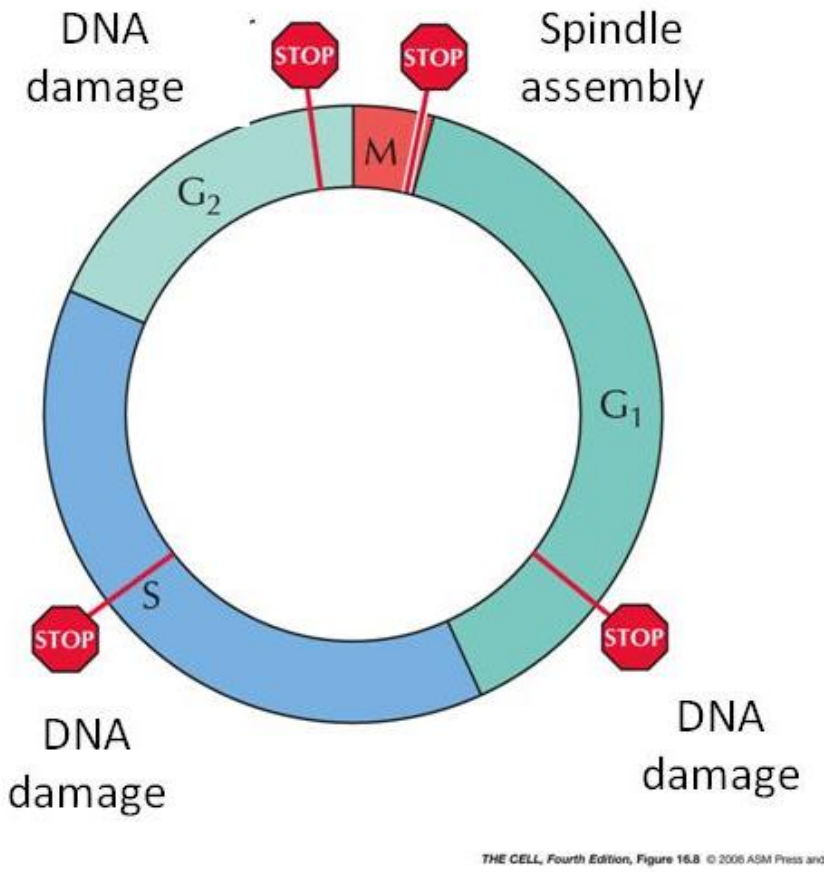
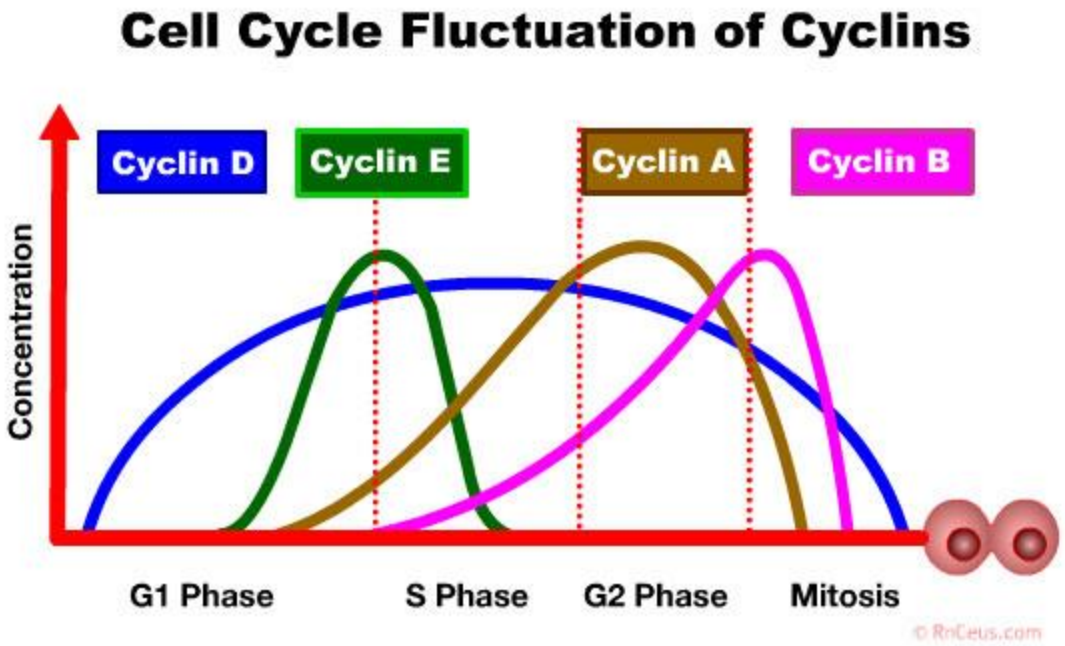
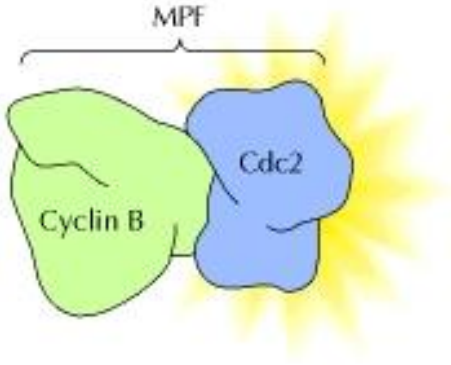


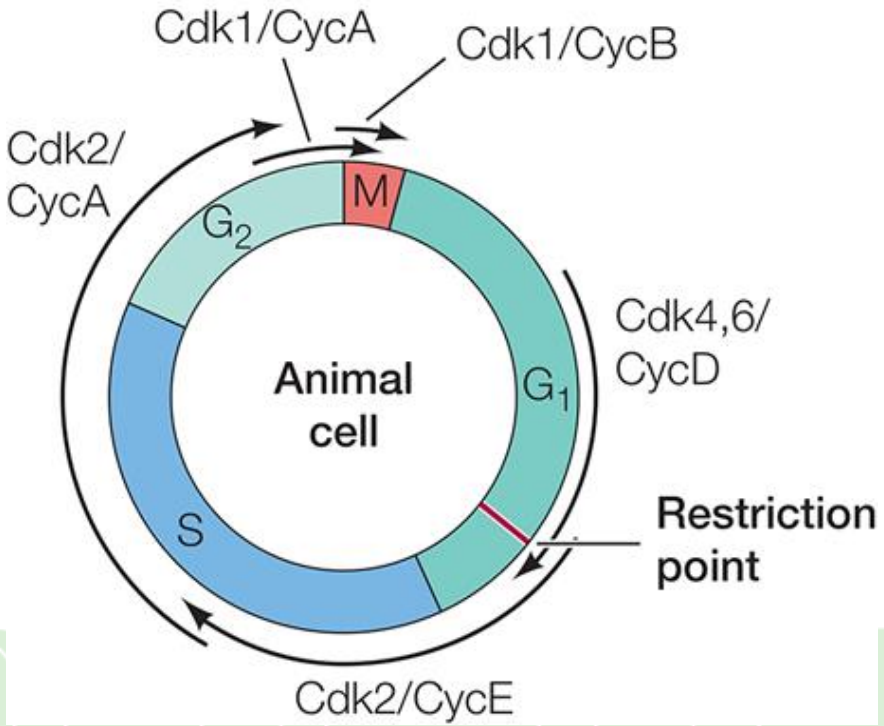
THE CELL, Fourth Edition, Figure 16.8 © 2006 ASM Press and

Regulating cyclin-Cdk dimers of the cell cycle

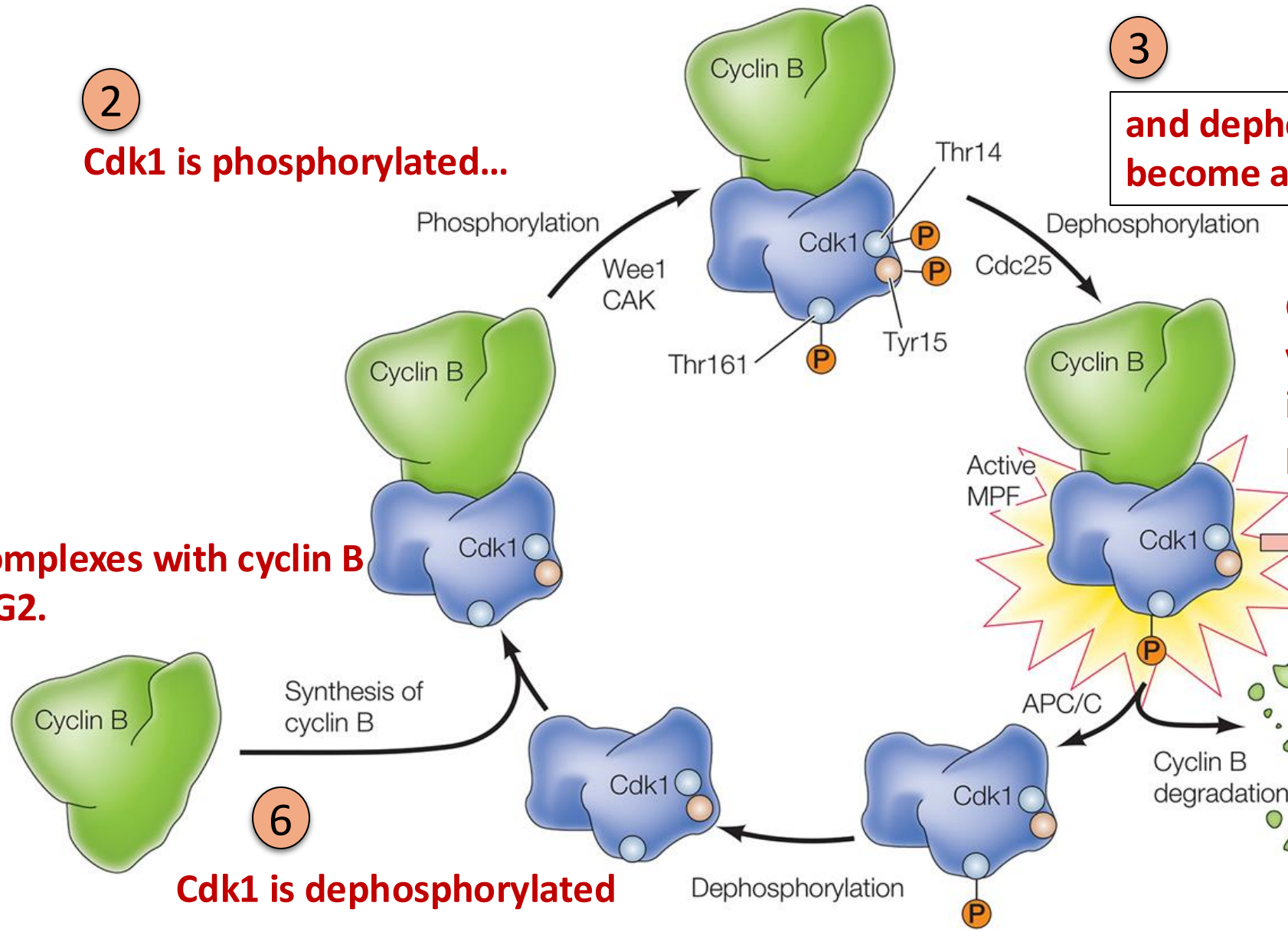
- Cyclins: proteins that go through cycles of synthesis (starting from the beginning of the interphase peaking at the beginning of mitosis) and degradation (by the end of mitosis).
- Cyclin-dependent kinases (Cdk's): get activated when dimerized with cyclins.







Example of regulation of cell cycle progression



1

Cdk1 complexes with cyclin B during G2.

2

Cdk1 is phosphorylated…

3

and dephosphorylated by CDC25 to become active

4

Cdk1 can phosphorylate a variety of target proteins that initiate entry into the M phase

5

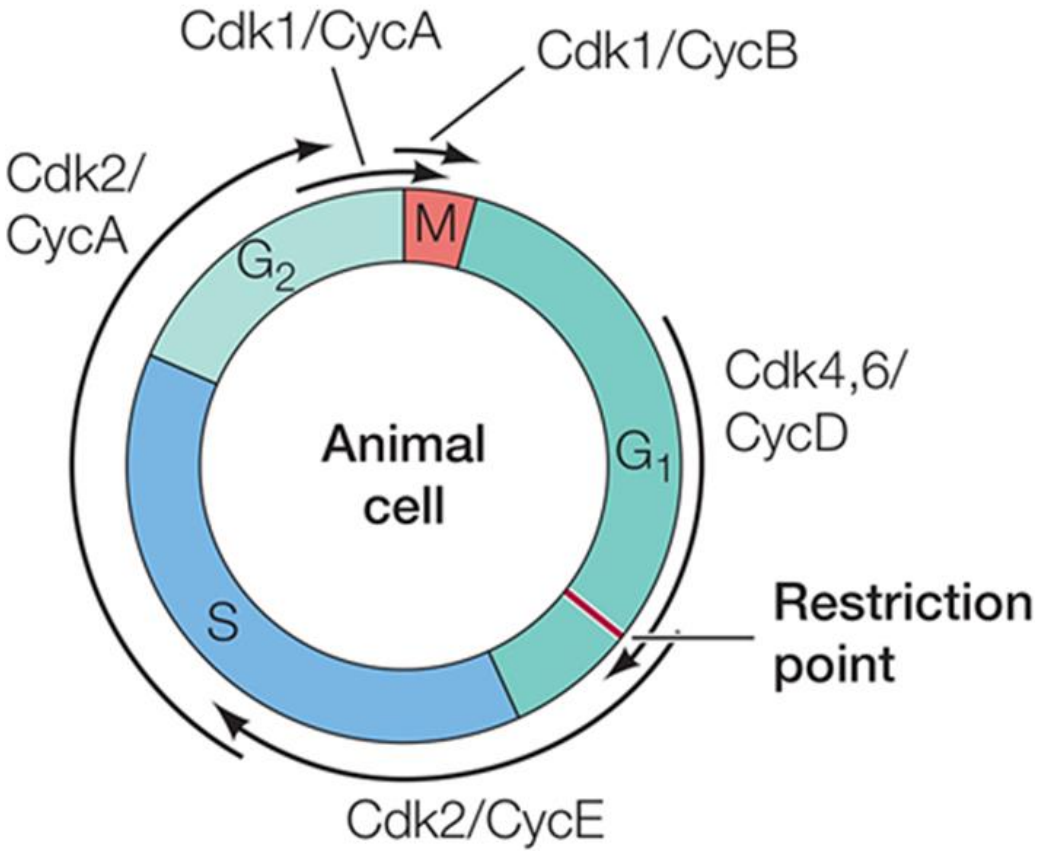
Proteolytic degradation of cyclin B terminates complex activity

6

Cdk1 is dephosphorylated

The different regulatory complexes

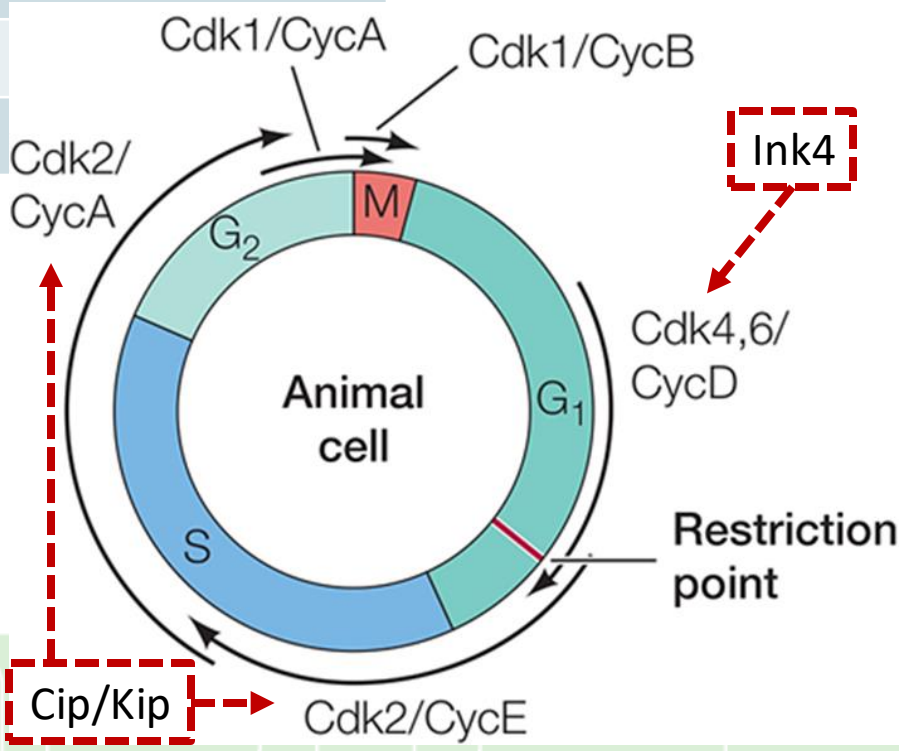
- Complexes of Cdk4 and Cdk6 with cyclin D control progression through the G1 restriction point.
- Cdk2/cyclin E complexes are required for the G1 to S transition.
- Cdk2/cyclin A complexes are required for progression through S phase and G2.
- Cdk1/cyclin A and Cdk1/cyclin B complexes drive the G2 to M transition and progression through mitosis.



Cdk's are selectively inhibited

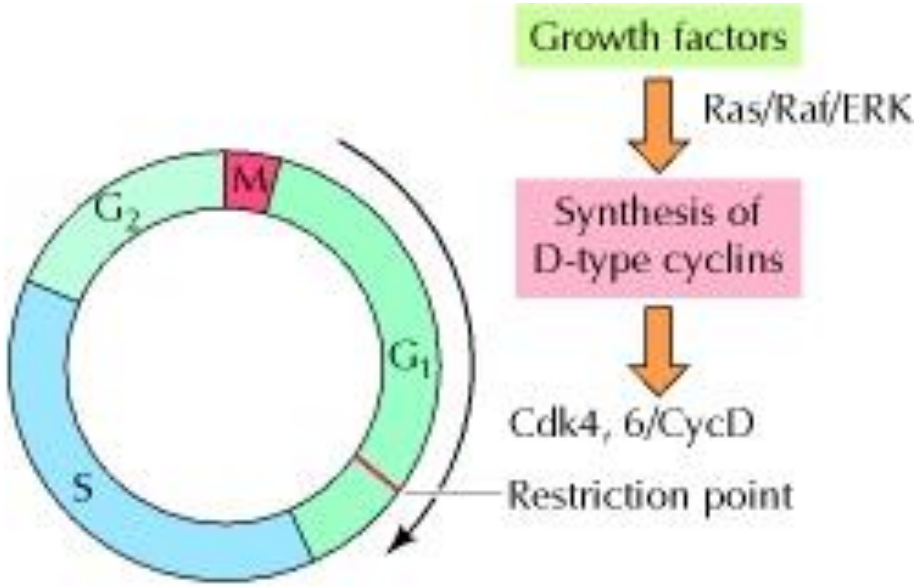
- The activities of Cdks are selectively regulated by Cdk inhibitors (CKIs).
- They belong two families of Cdk inhibitors.

Inhibitor	Cdk or Cdk/cyclin complex	Cell cycle phase inhibited
Ink4 family (p15, p16, p18, p19)	Cdk4 and Cdk6	G1
Cip/Kip family (**p21, p27**, p57)	Cdk2/cyclin E	G1
	Cdk2/cyclin A	S, G2



Cells signaling and cell cycle

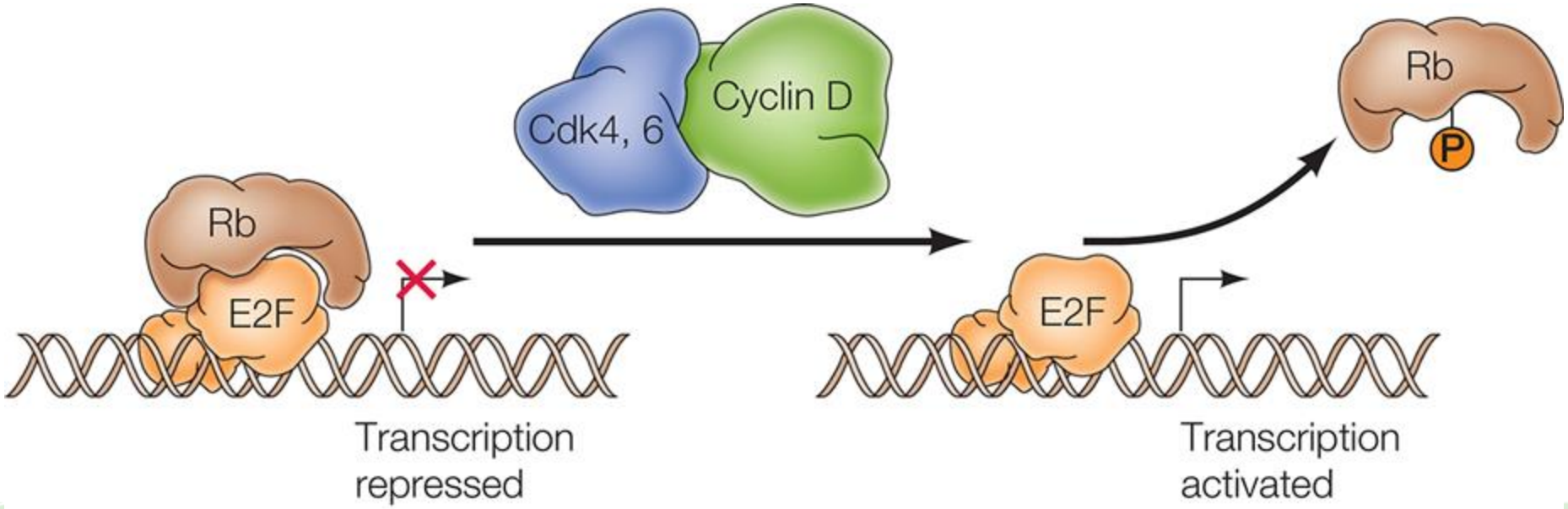
- Growth factors regulate cell cycle progression through the G1 restriction point by inducing the synthesis of cyclin D via the Ras/Raf/ERK signaling pathway.
- Defects in cyclin D regulation lead to the loss of growth regulation characteristic of cancer cells.



- Also, mutations that inactivate the Ink4 Cdk inhibitors are commonly found in human cancer cells.
  - An example is Rb protein (a tumor suppressor gene).

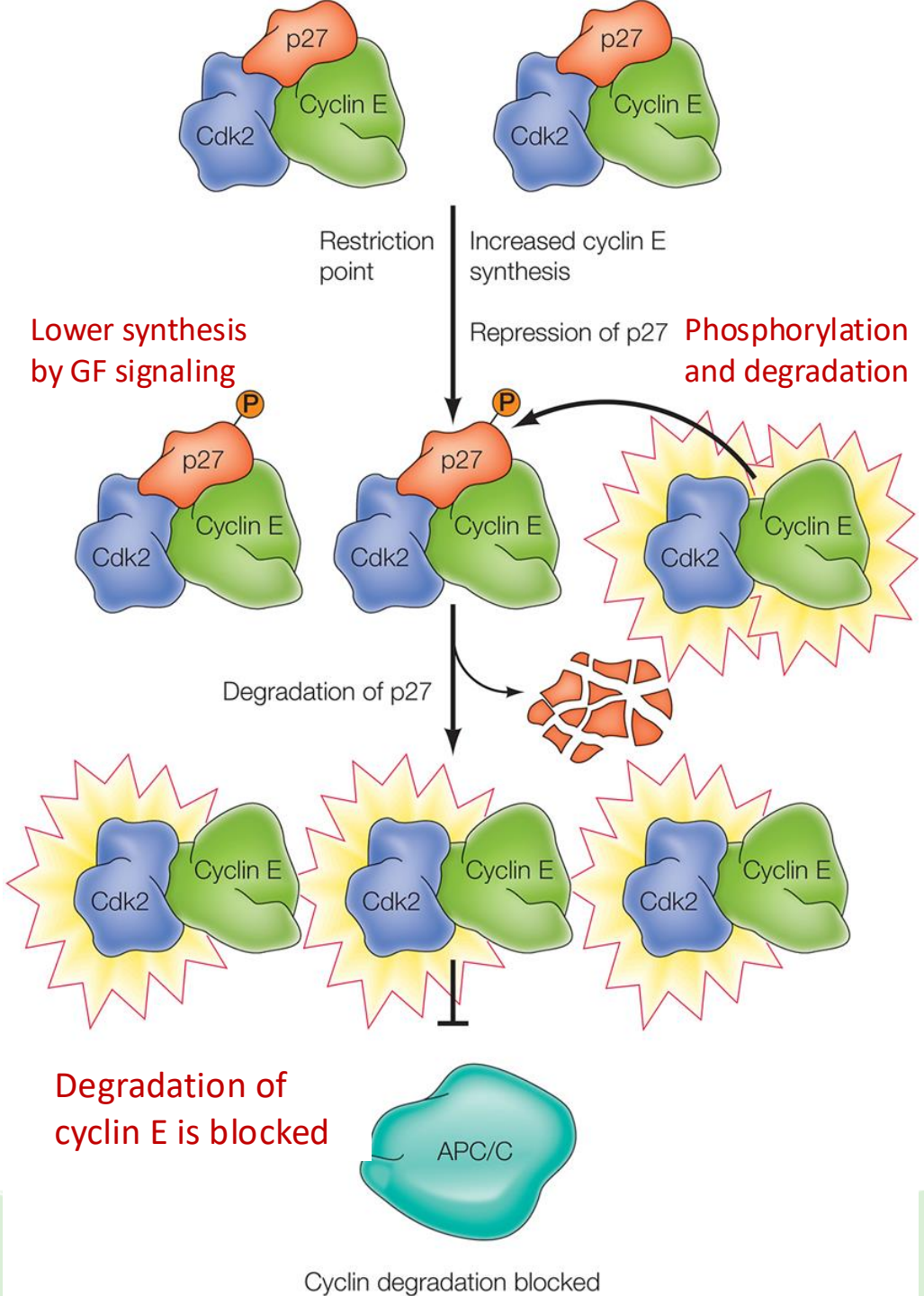
Retinoblastoma

- When unphosphorylated, Rb protein binds to members of the E2F family of transcription factors repressing the transcription of many genes involved in cell cycle progression such as cyclin E.
- E2F is freed when Rb is phosphorylated by Cdk4,6/cyclin D stimulating cell cycle progression through restriction point.



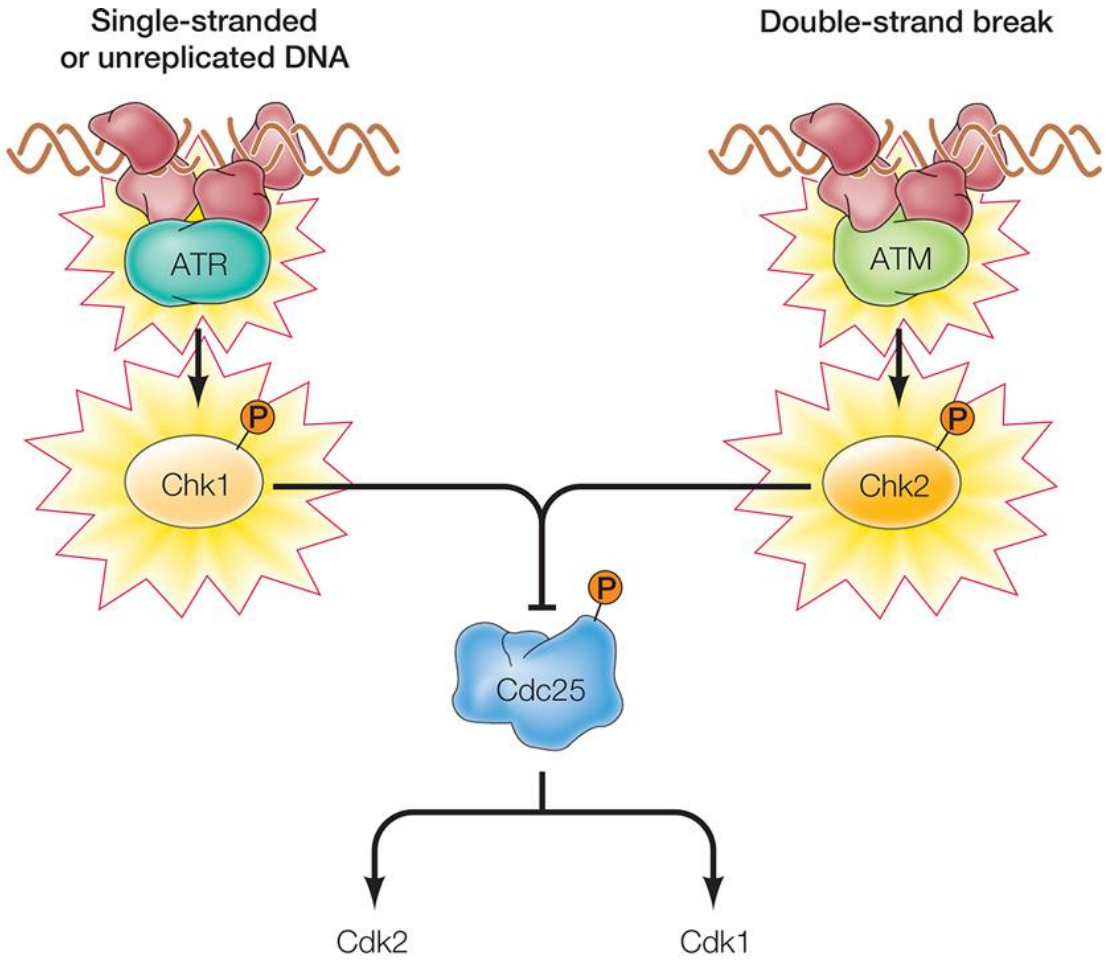
Activation of Cdk2/cyclin E

- The Cdk inhibitor p27 inhibits cdk2/cyclin E complexes.
- When cells pass through the restriction point, (1) the synthesis of cyclin E is induced via activation of E2F.
- Also, (2) growth factor signaling inhibits the synthesis of p27.
- (3) Activated Cdk2 phosphorylates and targets p27 for degradation, resulting in further activation of Cdk2/cyclin E complexes.
- (4) Cdk2/cyclin E also inhibits ubiquitination, and degradation of cyclin E.



ATR and ATM

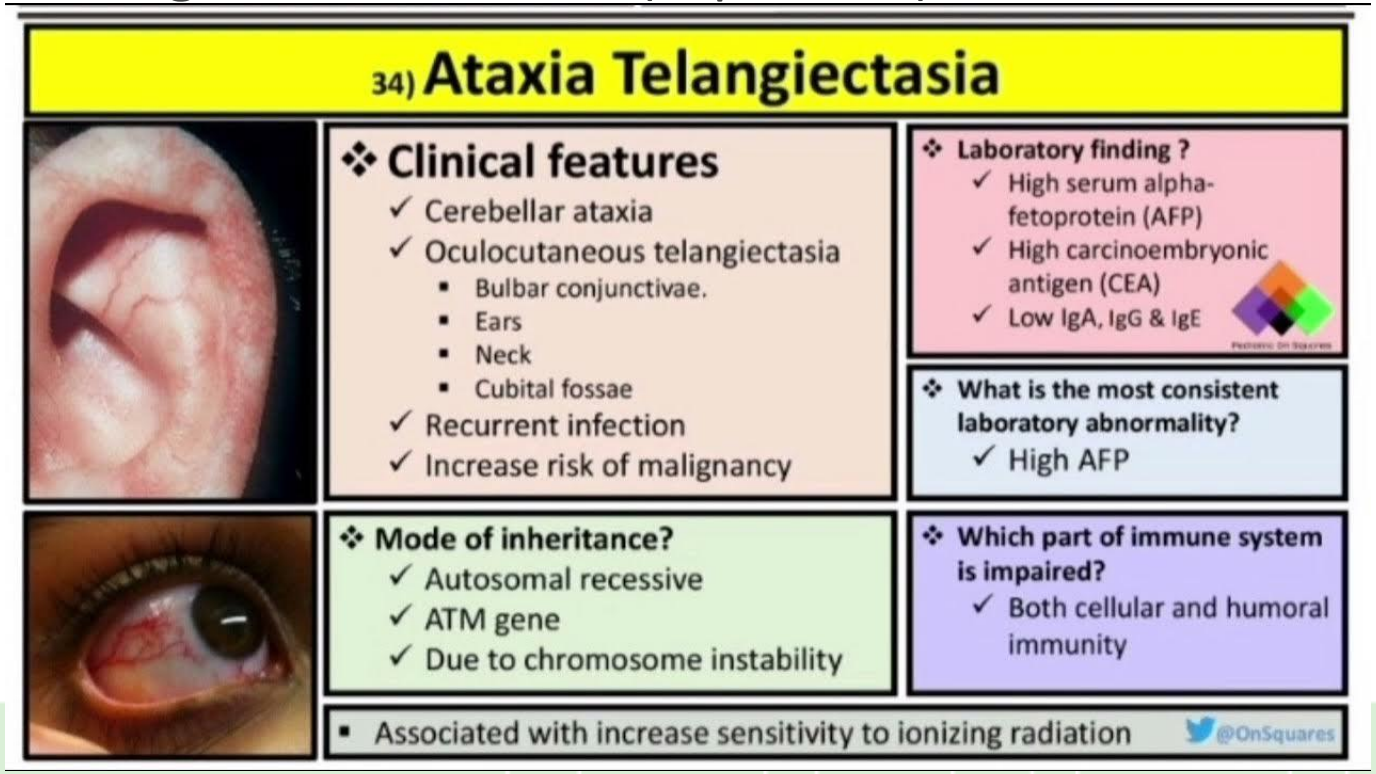
- If DNA is damaged, the cells undergo cycle arrest mediated by two protein kinases, ATR and ATM.
- Both are activated in response to single- and double-stranded DNA damage and activate:
  - cell cycle arrest
  - DNA repair and,
  - in some cases, programmed cell death
- Their activation leads to inhibition of Cdk1 and 2.



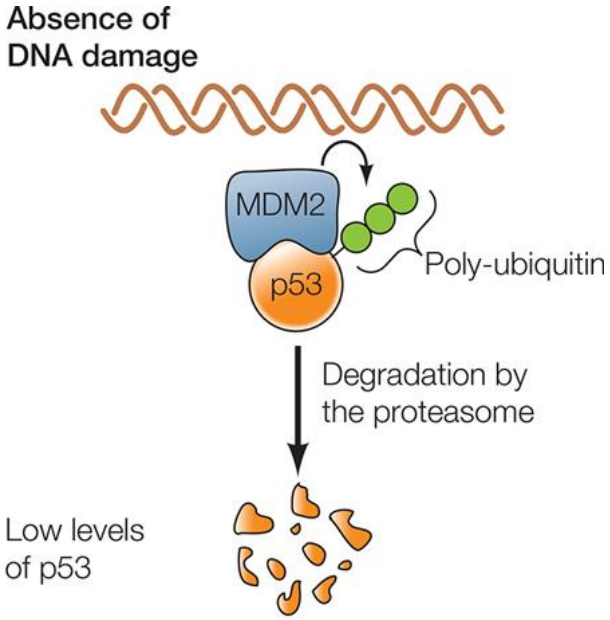
Ataxia-telangiectasia

Loss of muscle control-small, dilated blood vessels

- Defective ATM is responsible for the ataxia-telangiectasia, (defective nervous and immune systems and a high frequency of cancer).
  - Ataxia: uncoordinated movements, such as walking.
  - Telangiectasias: enlarged blood vessels (capillaries) below the surface of the skin.



Role of p53 in cell cycle arrest



In the absence of DNA damage, p53 is ubiquitinated for proteasomal degradation keeping p53 levels low.

When DNA is damaged, ATM results in p53 phosphorylation blocking ubiquitination. In turn, p53 levels increase and p53 activates the transcription of the Cdk inhibitor p21, leading to inhibition of Cdk2/cyclin E complexes and cell cycle arrest.