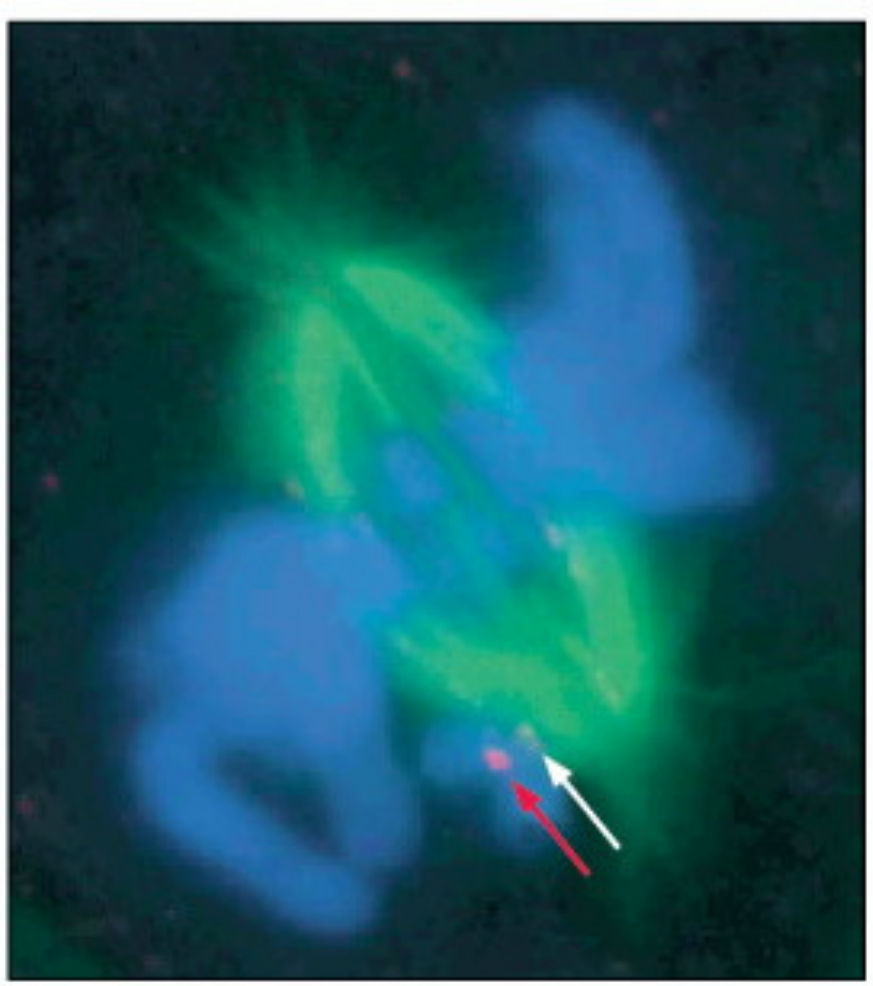
Cell Cycle I: Intracellular Control



The Cell Cycle

- Since this is review, we will not discuss at length the cell cycle itself.
- Focus on mechanisms of *control* that occur at specific stages.

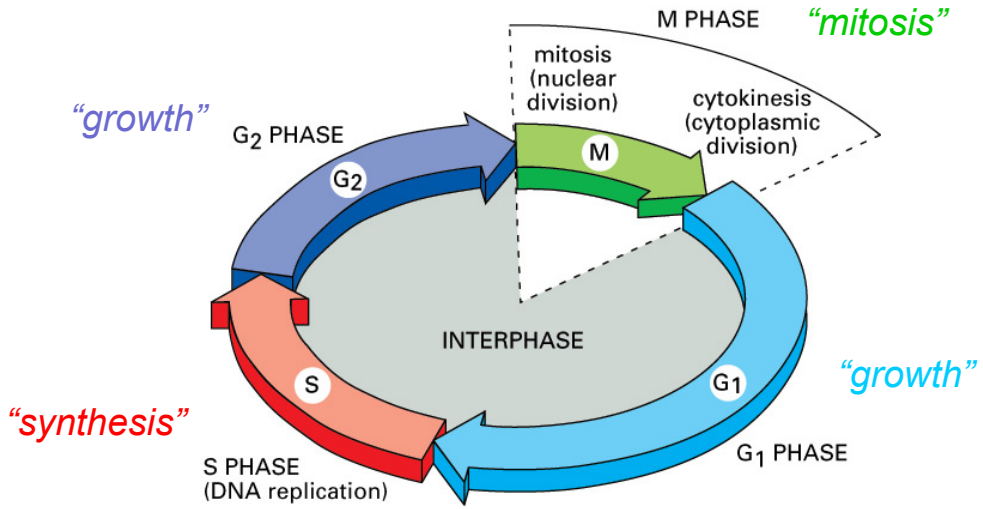


Figure 17–3. Molecular Biology of the Cell, 4th Edition.

Frog Egg

Zebrafish

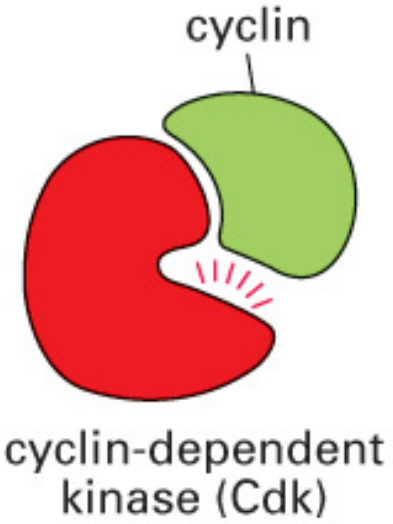
Karlstrom and Kane. 1996 *Development* 123:461.

Why Control the Cell Cycle?

- The cell cycle is a complex system of coordinated processes that must occur in a specific sequence.
- If performed incorrectly or out of sequence, results may be catastrophic.
- Regulatory proteins and biochemical switches control progression through the cell cycle.
- This system monitors intracellular and extracellular environments.

Cdks Control the Cell Cycle

- Cdk = “cyclin-dependent kinase”.
- Activity of cyclin (and thus Cdks) rises and falls with cell cycle.
- Molecular switches that regulate important events:
  - DNA replication
  - mitosis
  - chromosome segregation
  - cell proliferation



Classification of Cyclins and Cdks

Cyclins in all eukaryotes (4 major classes):

- G_1/S cyclins: bind Cdk near end of G_1 and lead cell into DNA replication.
- S-cyclins: bind Cdk during S phase and are required for DNA replication, control early mitotic events.
- M-cyclins: promote the events of mitosis.
- G_1-cyclins: (in most cells) promote passage through restriction point in late G_1.

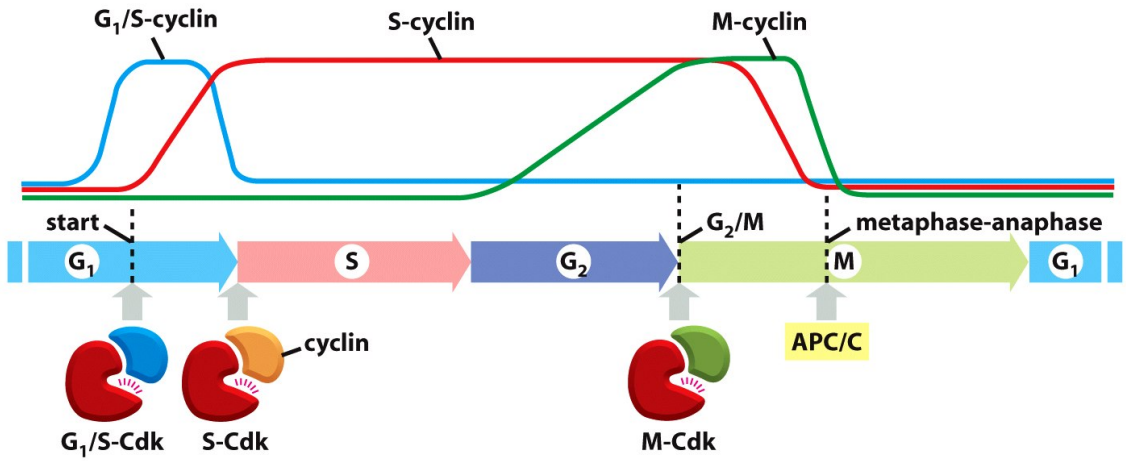


Figure 17-16 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Cdks are Protein Kinases

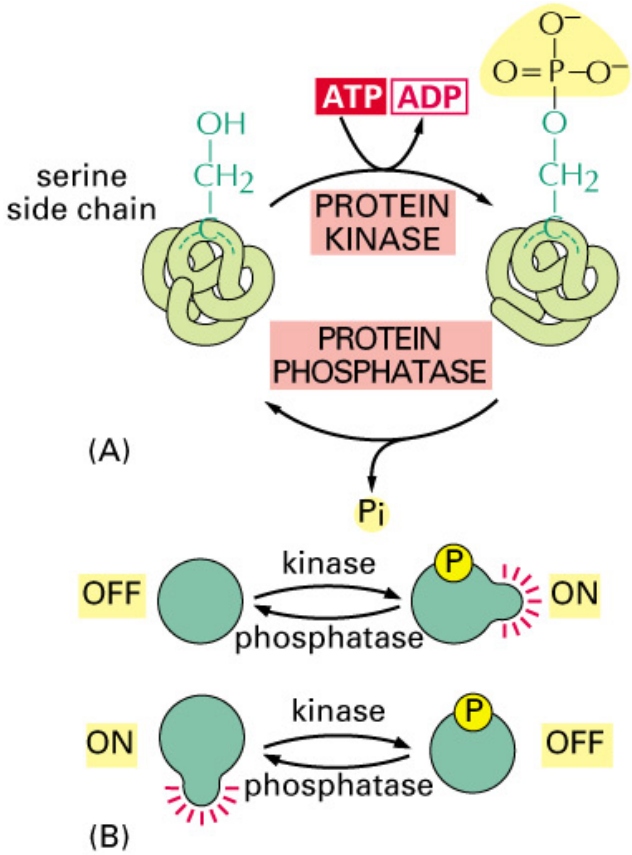


Figure 3–63. Molecular Biology of the Cell, 4th Edition.

Cdk Activity is Regulated

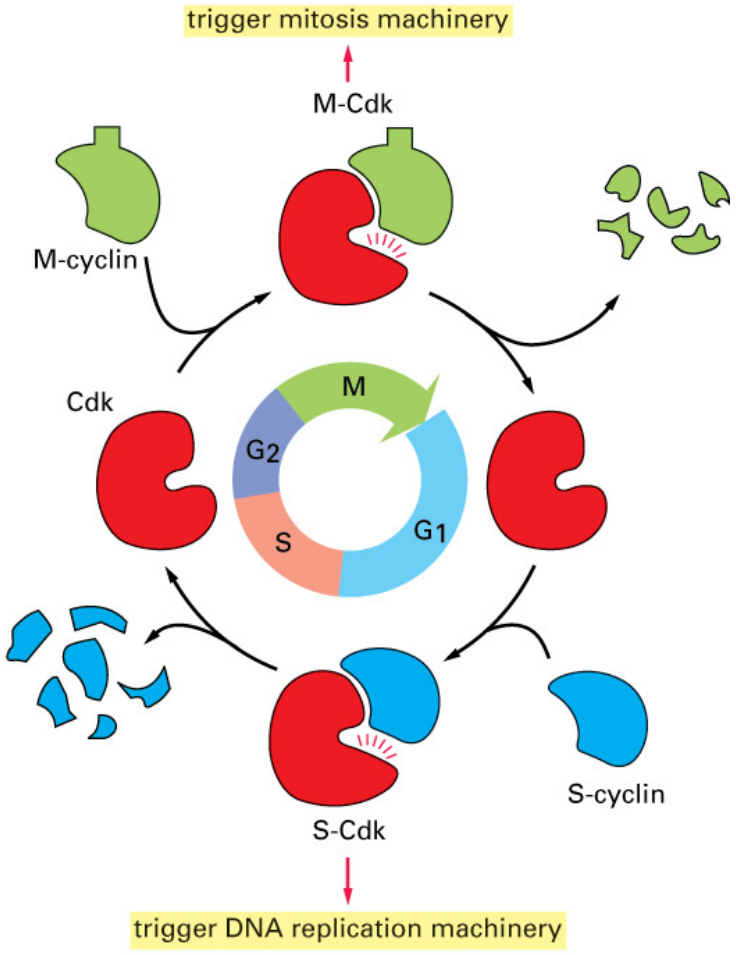


Figure 17–16. Molecular Biology of the Cell, 4th Edition.

Activation of Cdk-cyclin

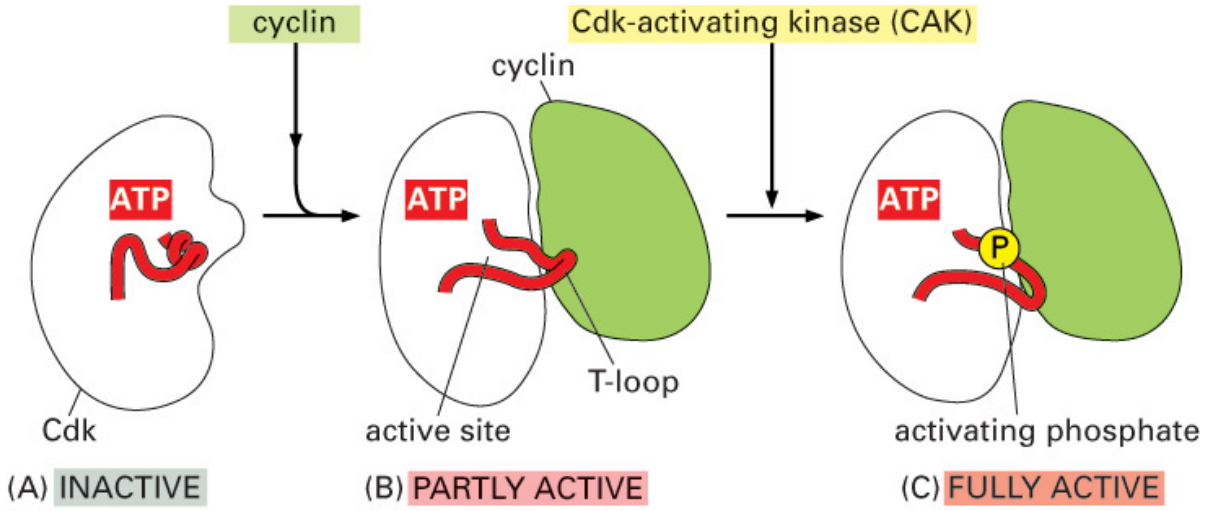


Figure 17–17. Molecular Biology of the Cell, 4th Edition.

Inhibition of Cdk

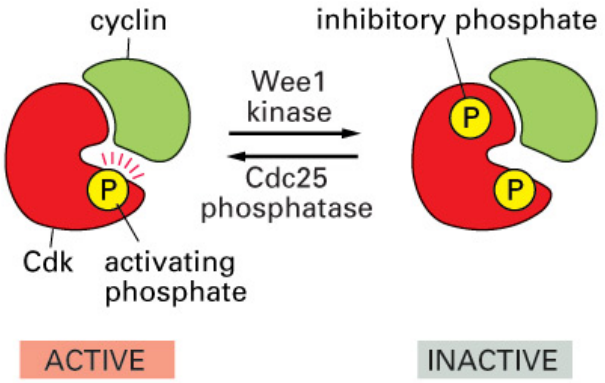


Figure 17–18. Molecular Biology of the Cell, 4th Edition.

e.g. M-Cdk

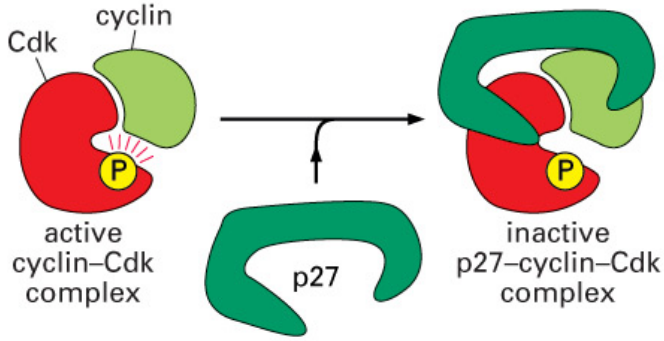
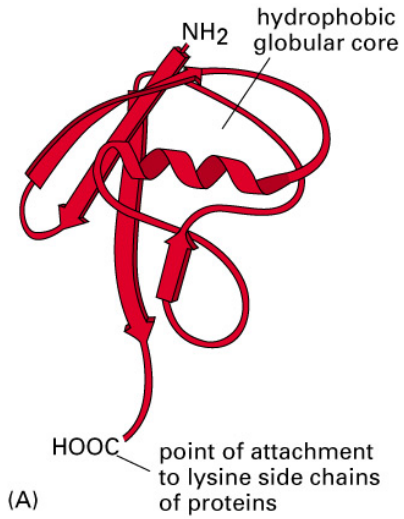


Figure 17–19. Molecular Biology of the Cell, 4th Edition.

p27 is a CKI

Ubiquitin and Protein Degradation

Ubiquitin



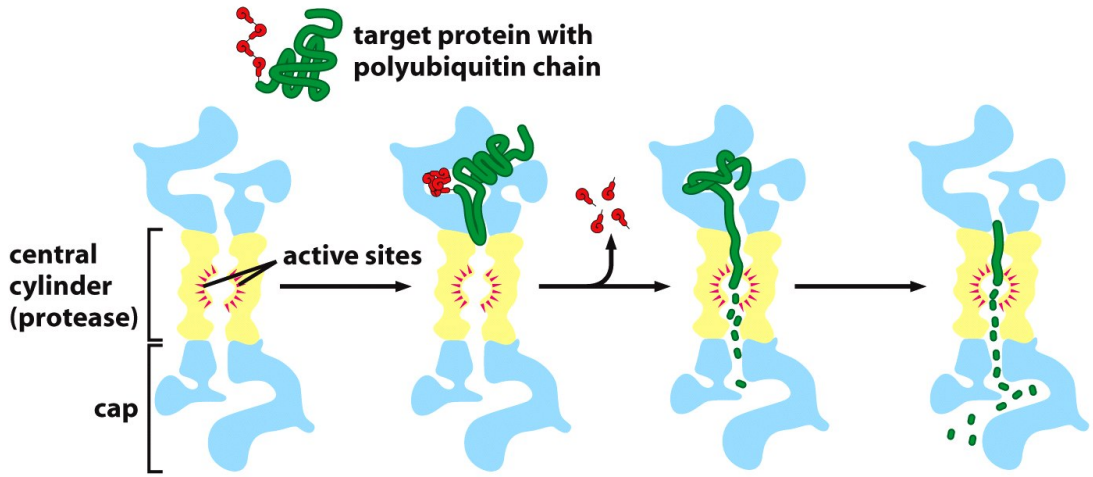


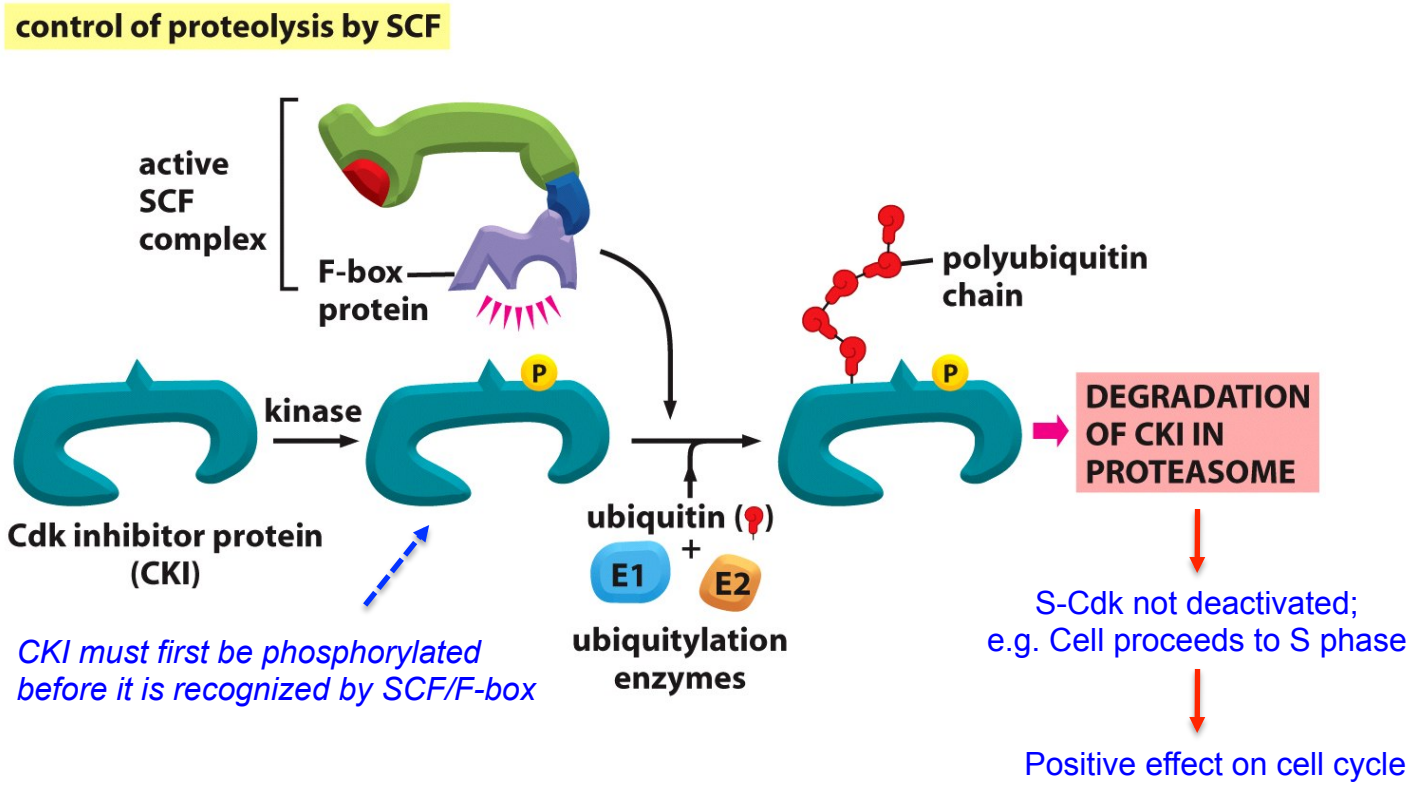
Figure 6-90 *Molecular Biology of the Cell, 5th ed.* (2008)

The proteasome

A ubiquitin ligase is required to catalyze addition of a polyubiquitin chain to a protein

SCF and APC are Ubiquitin Ligases

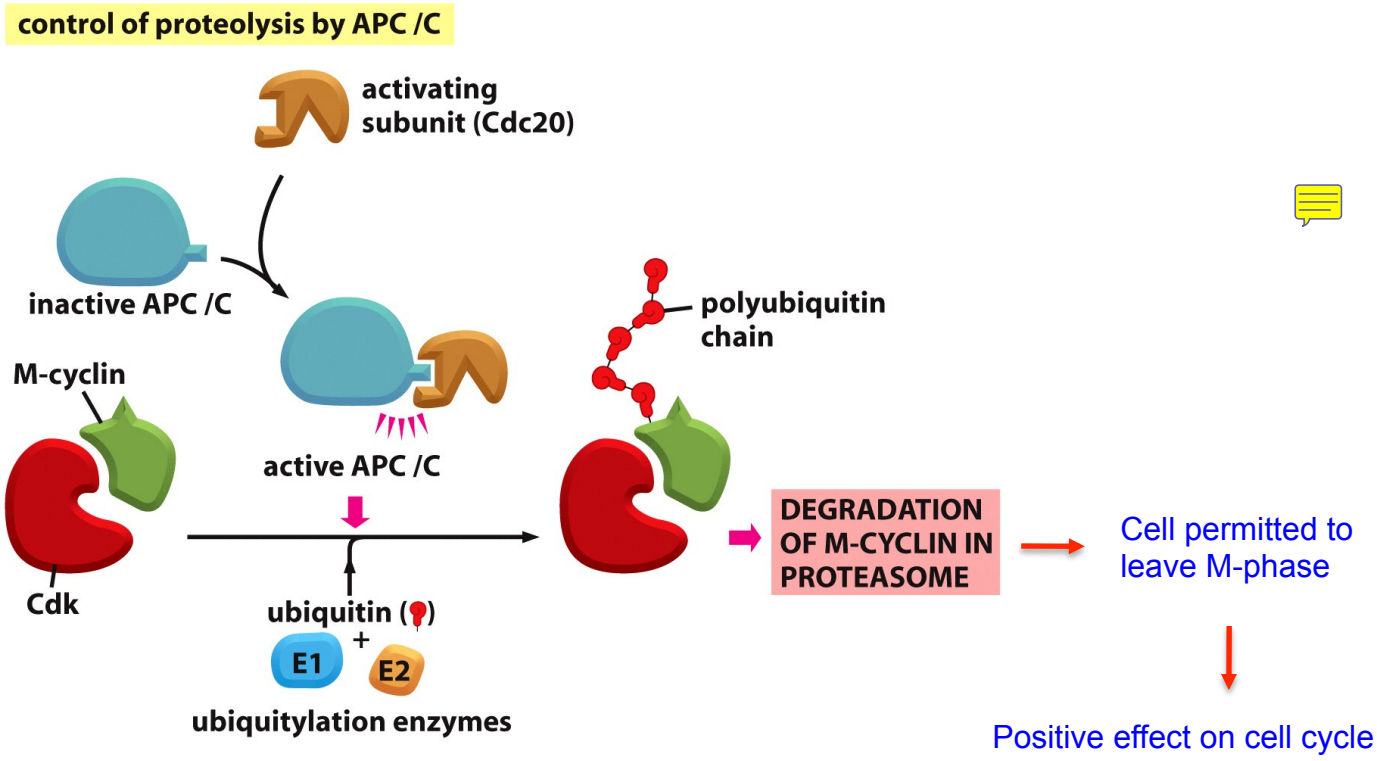
- SCF can lead to destruction of G_1/S cyclins (see slide 5).
- SCF can lead to destruction of CKI (e.g. below and slide 5, 9).



Skp/**C**ullin/**F** box family of proteins; **A**naphase **P**romoting **C**omplex

SCF and APC are Ubiquitin Ligases

- APC can lead to destruction of securin, leading to chromatid separation (see slide 17).
- APC can lead to destruction of M-cyclin (e.g. below and slide 5).



Skp/**C**ullin/**F** box family of proteins; **A**naphase **P**romoting **C**omplex

SCF and APC are Active During Different Stages

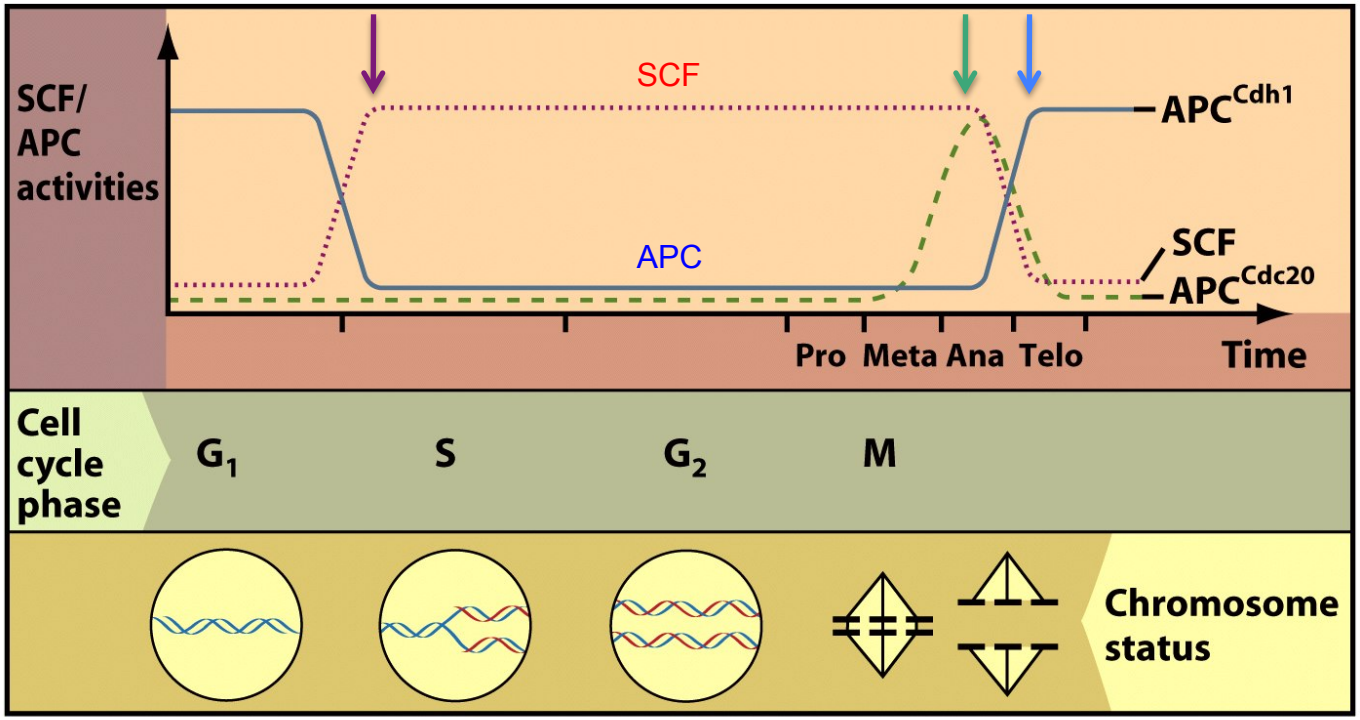


Figure 14-26a Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

(-)

APC-Cdc20 activation → ↓M-cyclin (slide 5 and 12) → ↓M-Cdk → ↑APC-Cdh1 (above) → Keeps M-cyclin levels low (slide 5) and cell leaves M-phase

APC-Cdc20 activation → Separase activation and anaphase (slide 17)

Activation of M-Cdk Triggers Mitosis

Here, we are in the latter stages of G_2 on the brink of mitosis…

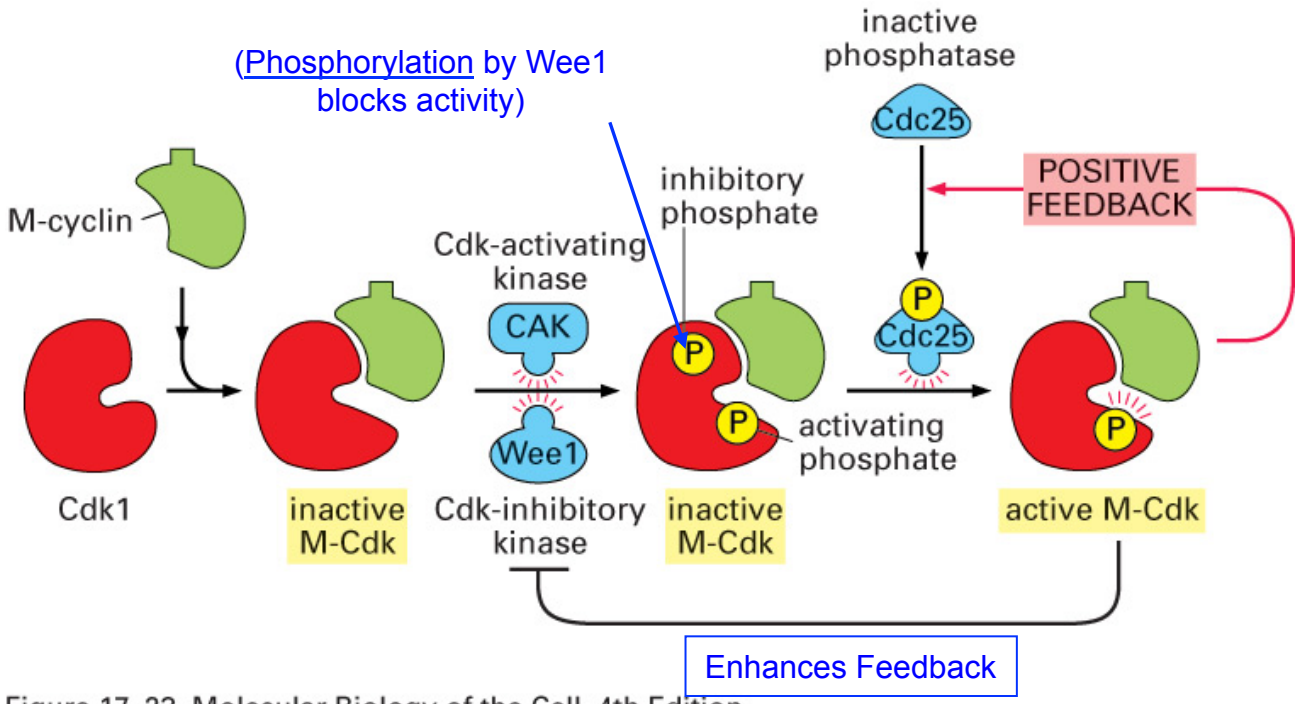


Figure 17–23. Molecular Biology of the Cell, 4th Edition.

S-Cdk phosphorylates (activates) Cdc25 during M-phase (see slide 5)

“Checkpoints”

1. DNA replication checkpoint
2. Spindle attachment checkpoint
3. DNA damage checkpoints (several)

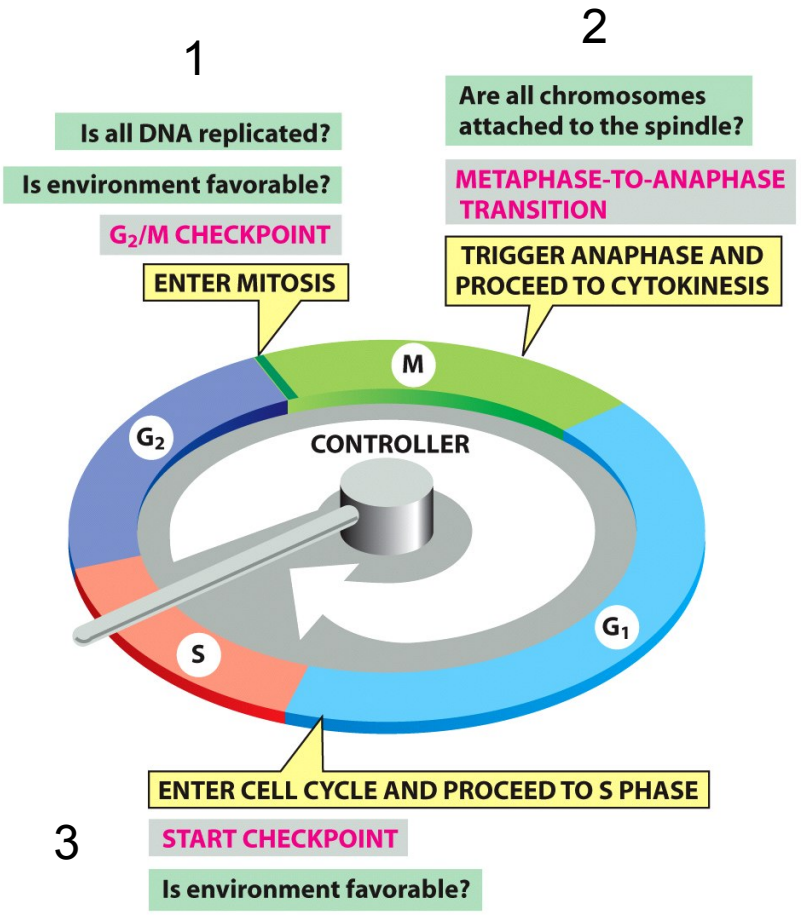


Fig. 17-14. Alberts, 5th ed.

DNA Replication Checkpoint

Detection of unreplicated DNA

Cdc 25 not activated; M-Cdk activation is blocked

(See slide 14)

Cell does not progress into mitosis

Chromatid Separation

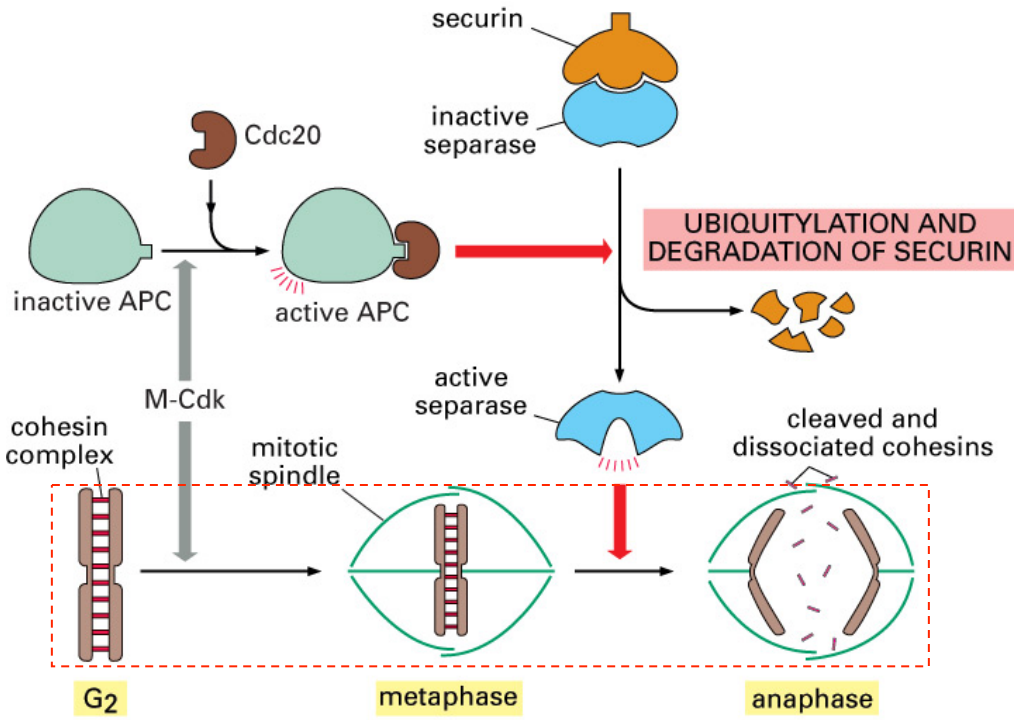
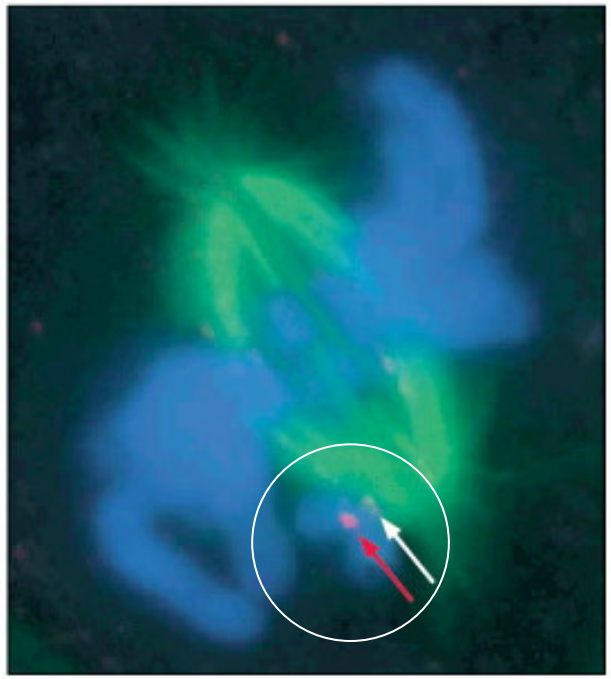


Figure 17–26. Molecular Biology of the Cell, 4th Edition.

Spindle Attachment Checkpoint

Unattached
kinetochore
↓
Mad2 binds
↓
Cdc20-APC
activation blocked
↓
No chromatid separation



Nondisjunction

"Mad" = mitotic arrest deficient

DNA Damage Checkpoint (G_1)

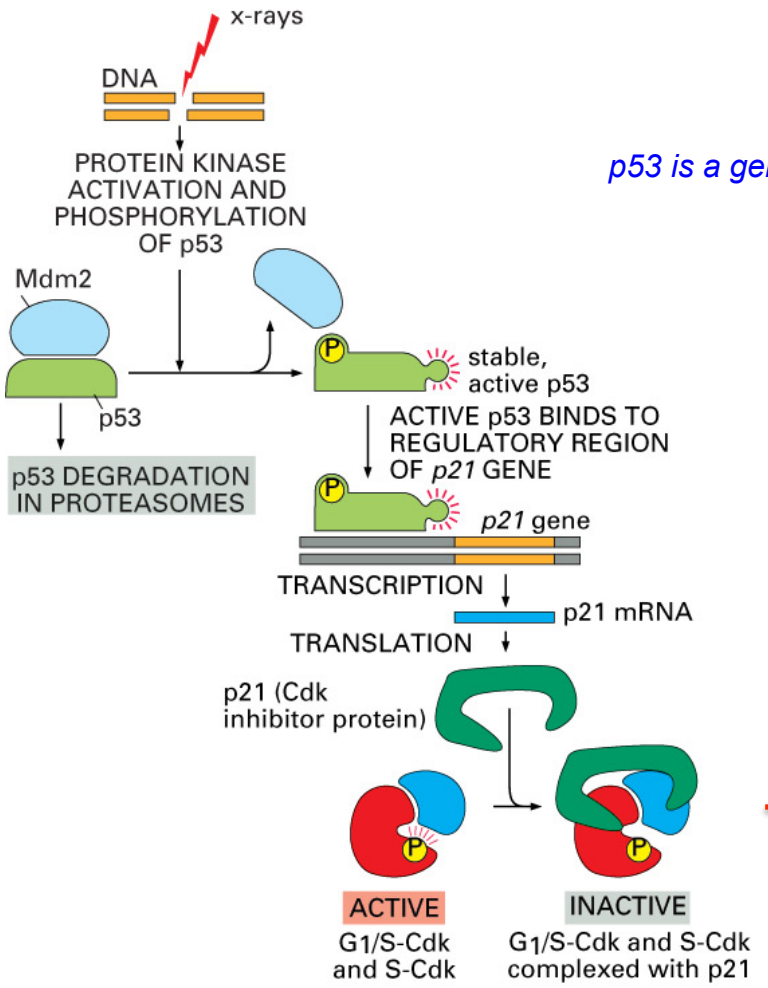


Figure 17–33. Molecular Biology of the Cell, 4th Edition.

p53 is a gene regulatory protein, GRP

Negative effect on cell cycle
Cell does not enter S-phase