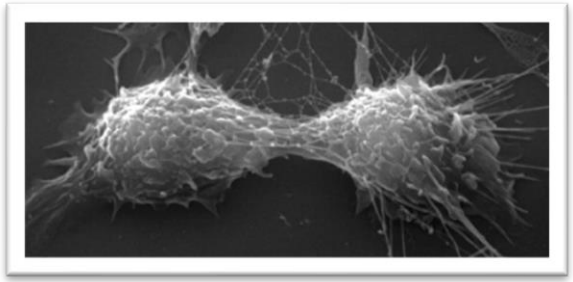
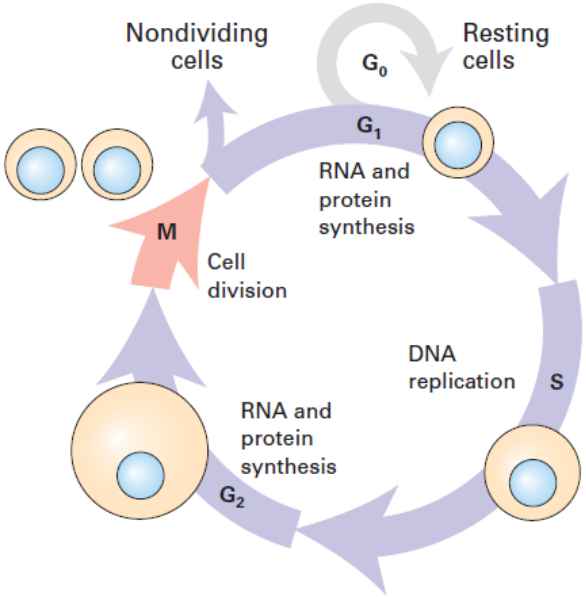
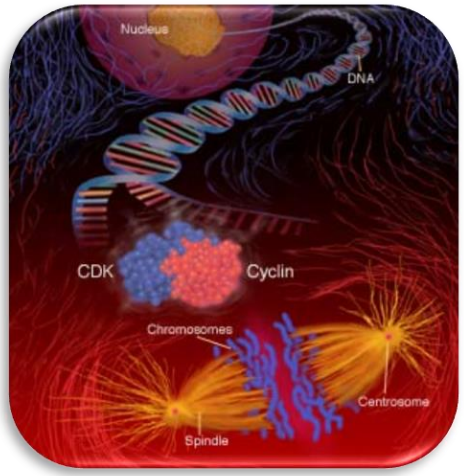
Cell growth and development;

1. Regulation of eukaryotic cell cycle







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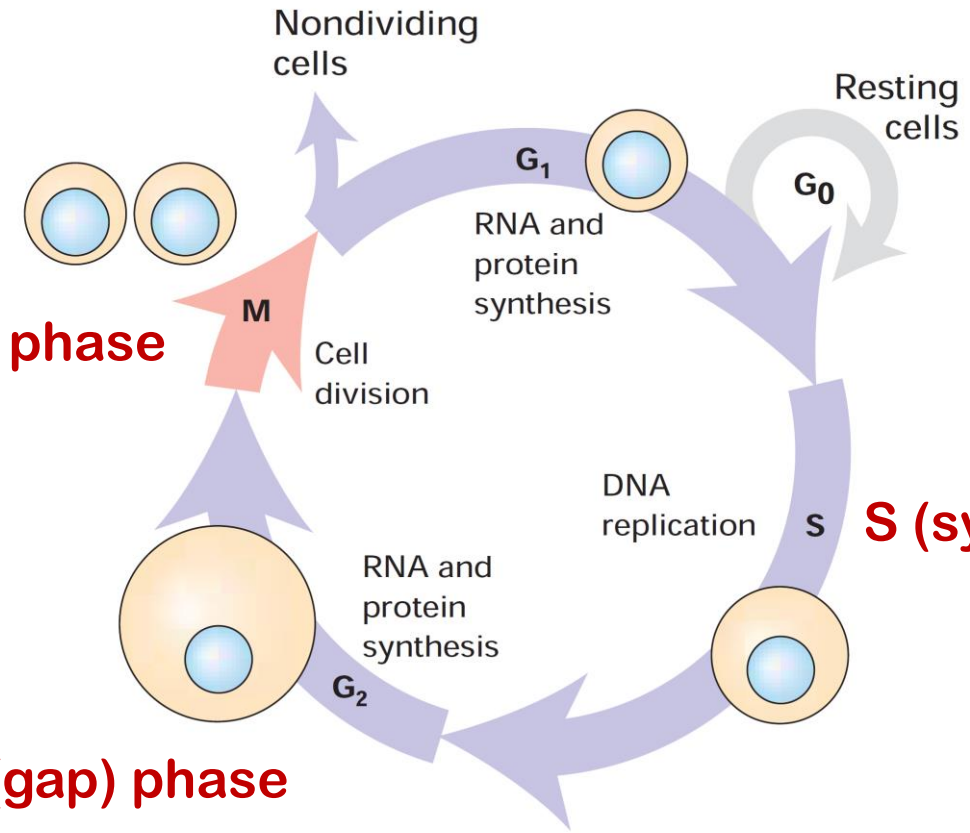
Contents

Eukaryotic cell division

- The simplest type of reproduction → the division of a "parent" cell into two "daughter" cells



M (mitotic) phase

S (synthesis) phase

G (gap) phase

Frequency of cell division

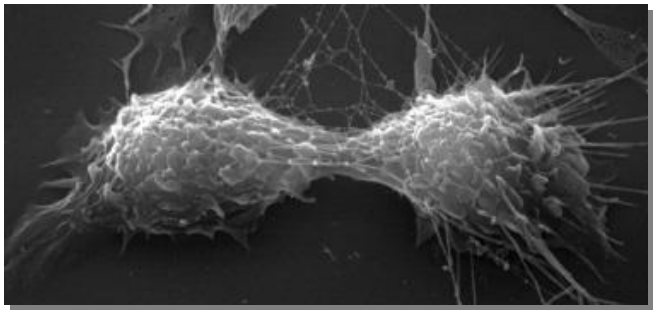
- **Varies by cell type**
  - **embryo**

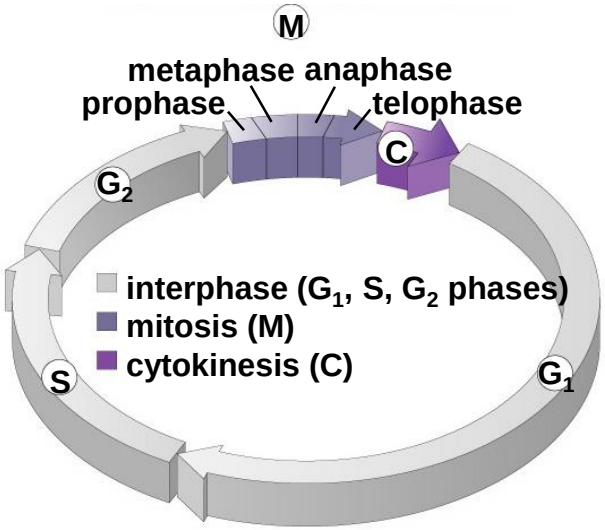
    .....
  - **skin cells**

    .....
  - **liver cells**

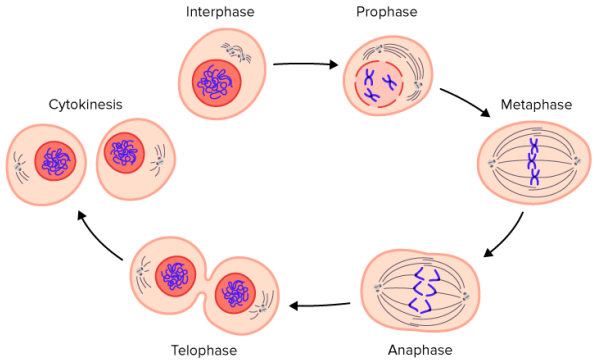
    .....
  - **mature nerve cells & muscle cell**

    .....

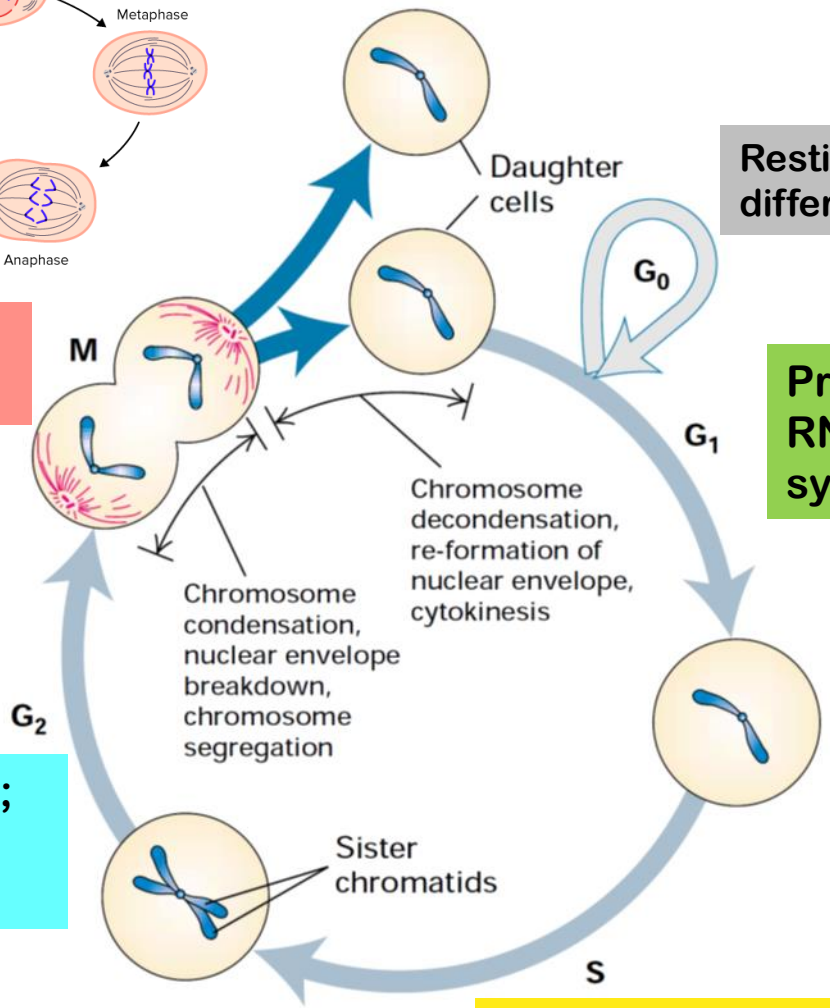




Overview of the Cell Cycle



chromosomes separation and cell division



Resting; non-dividing, differentiated state

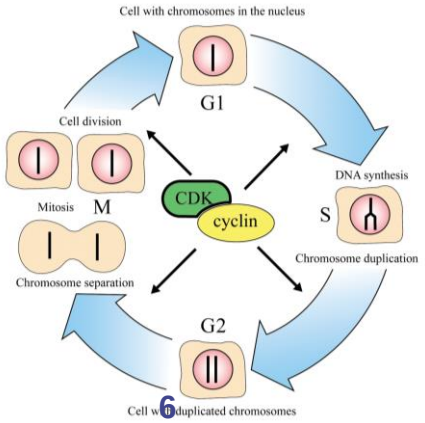
Preparation for S phase; RNA and protein syntheses

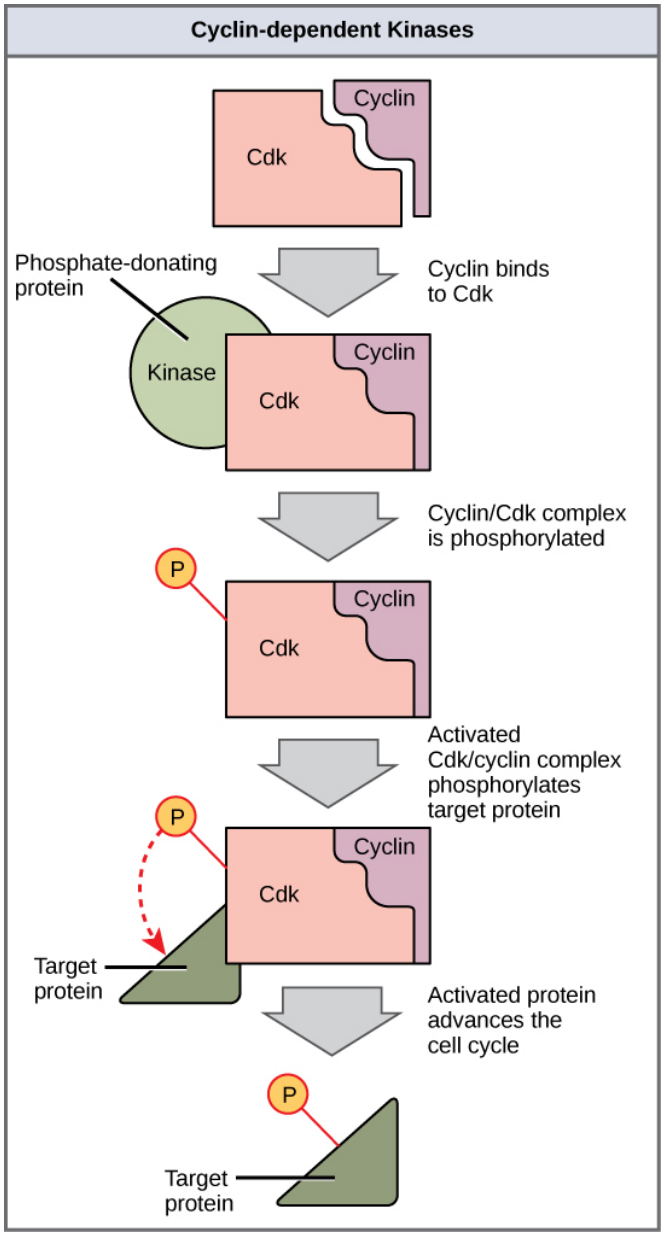
Preparation for M phase; RNA and protein syntheses

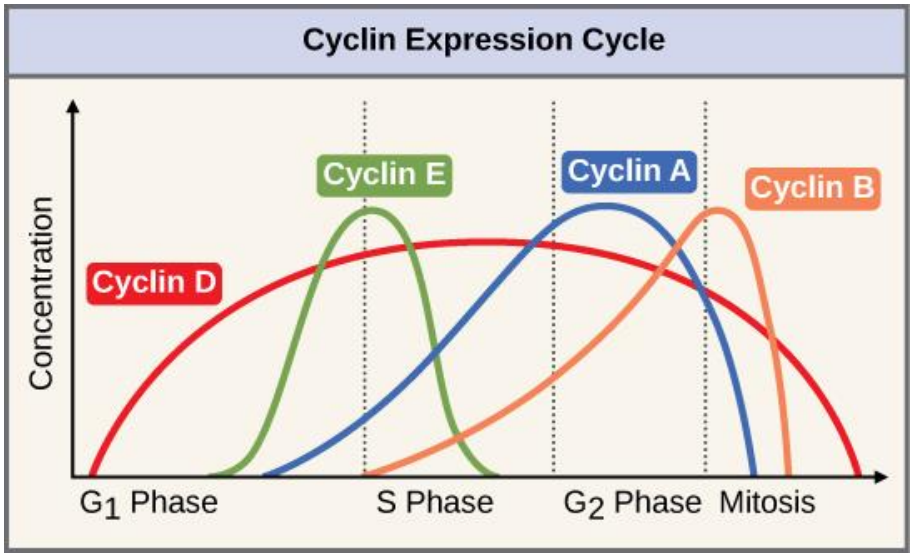
DNA synthesis and chromosome replication

Cyclins & CDKs drive cell from one phase to next in cell cycle.

- **Cyclins**
  - regulatory proteins
  - levels cycle in the cell
- **Cdks**
  - cyclin-dependent kinases
  - phosphorylates cellular proteins
    - activates or inactivates proteins
- **Cyclin-CDK complex**
  - triggers passage through different stages of cell cycle







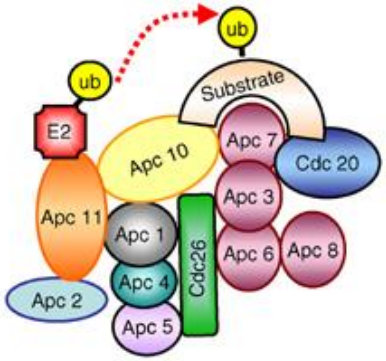
	G1	G1/S	S	G2	G2/M	M
CDK	4/6	2	2	1	1	1
Cyclin	D	E	A	A/B	A/B	A/B
Ub ligase		SCF			APC	

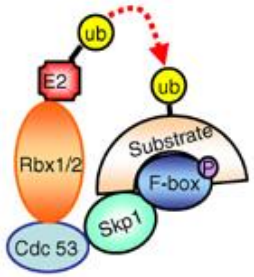
Ubiquitin-protein ligases participate in the timed destruction of cyclins and other key proteins and thereby ensure passage through the cell cycle is irreversible.

Skp, Cullin, F-box containing complex

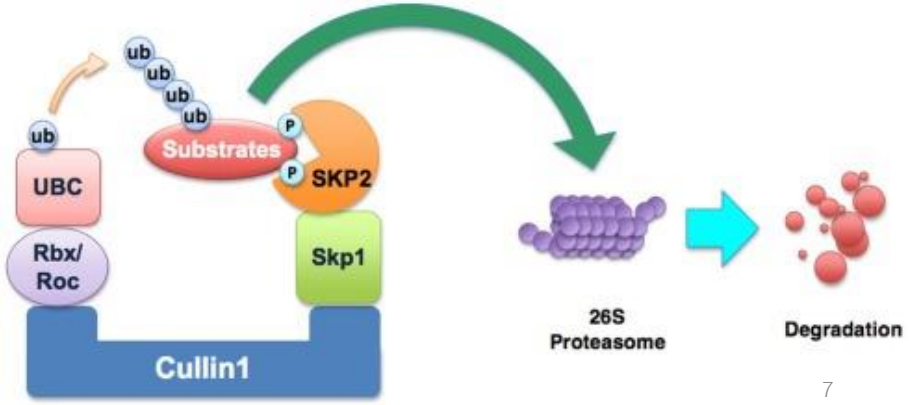
APC^{Cdc20} SCF

Anaphase-Promoting Complex

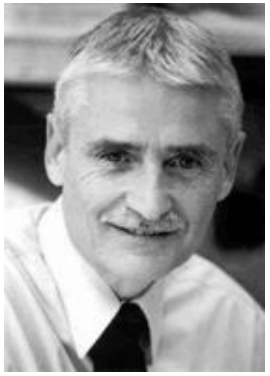




Regulating Protein Function by Degradation

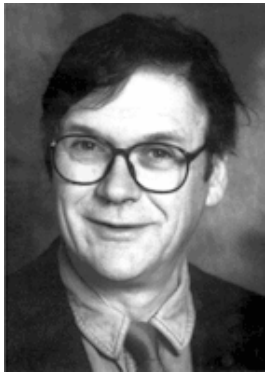


The Nobel Prize in Physiology or Medicine (2001) discoveries of "key regulators of the cell cycle"

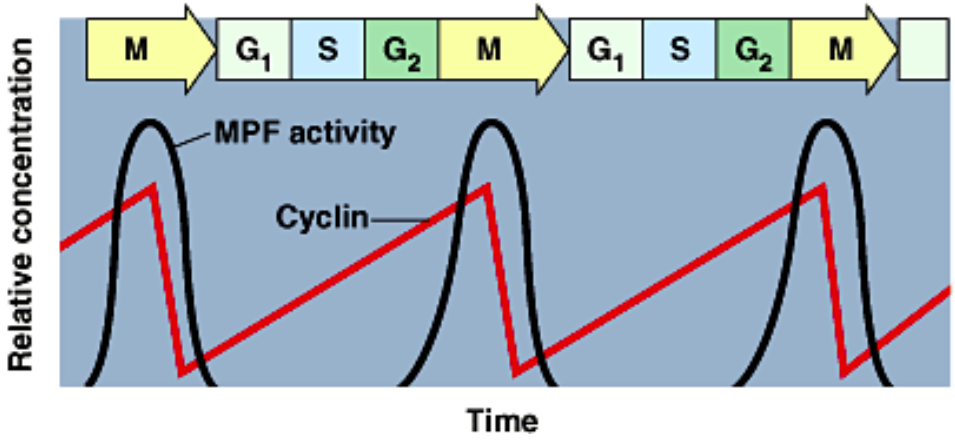


Leland H. Hartwell
checkpoints

Sir Paul M. Nurse
Cdks



Tim Hunt
Cyclins

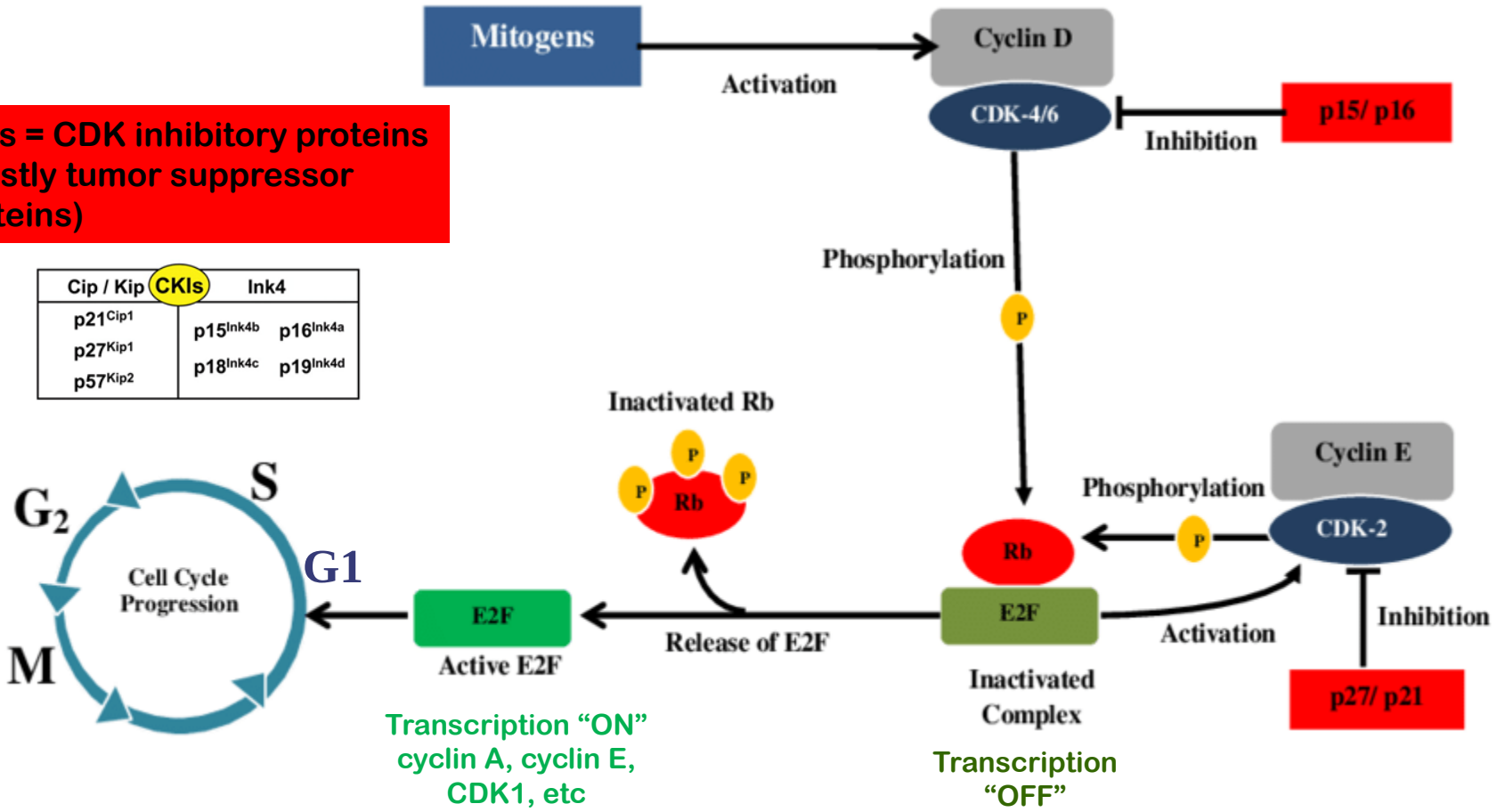


The rise and fall in levels of maturation promoting factor (MPF) and cyclin during the cell cycle.

How does cyclin-CDK complex control cell cycle?

CKIs = CDK inhibitory proteins (mostly tumor suppressor proteins)

Cip / Kip	CKIs	Ink4	
$p21^{Cip1}$		$p15^{Ink4b}$	$p16^{Ink4a}$
$p27^{Kip1}$		$p18^{Ink4c}$	$p19^{Ink4d}$
$p57^{Kip2}$			



Rb: Retinoblastoma, E2F transcription factor

Overview of checkpoint controls in the cell cycle

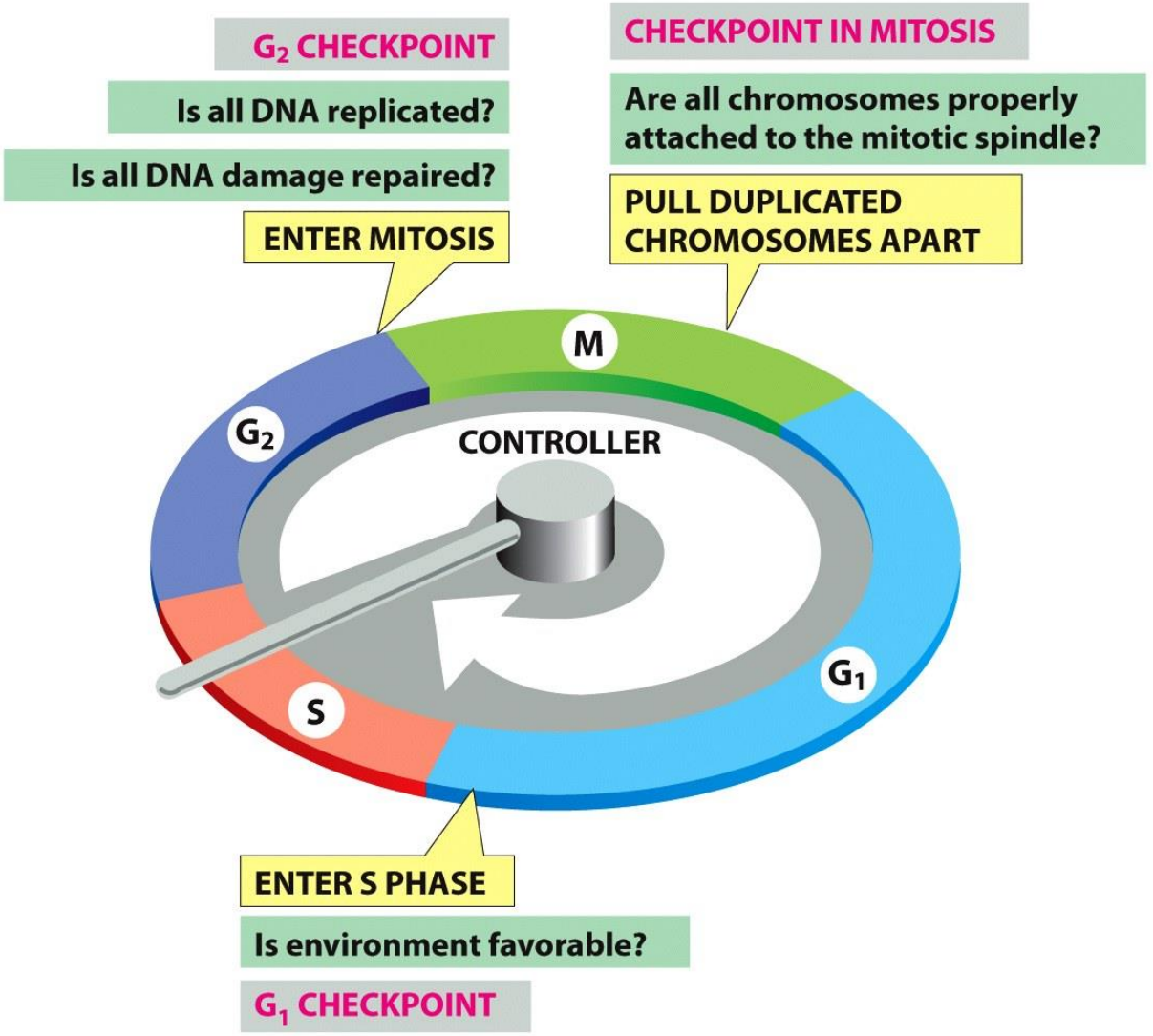
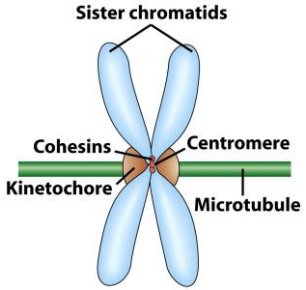


Figure 18-3 Essential Cell Biology 3/e (© Garland Science 2010)

Three components to checkpoint response



1. Damage or delay generates a signal

- DNA damage by drugs or irradiation
- Spindle defects or failure to attach a kinetochore

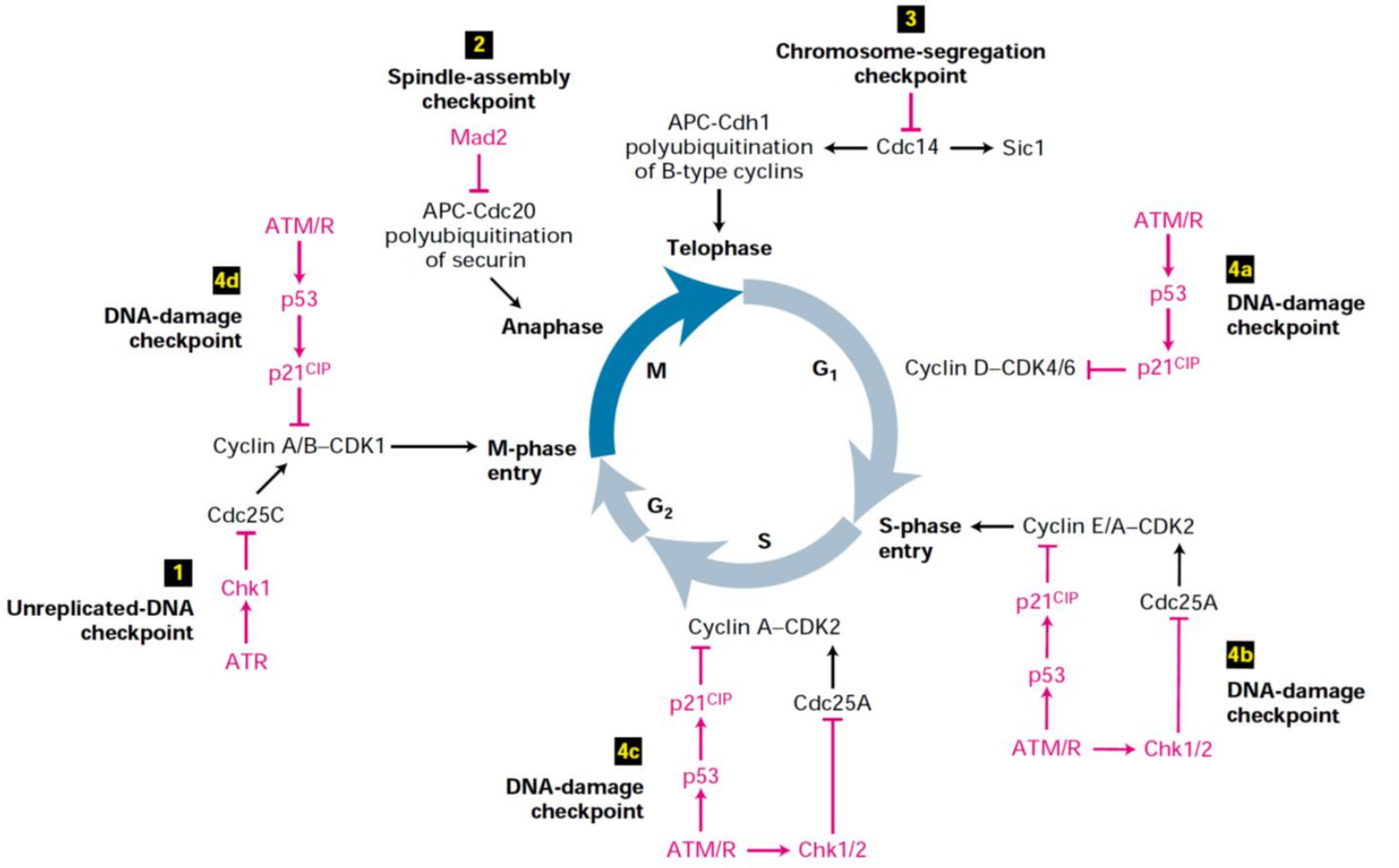
2. The signal is transmitted via a transducer

- For DNA damage, a kinase cascade

3. The signal is monitored by a receiver

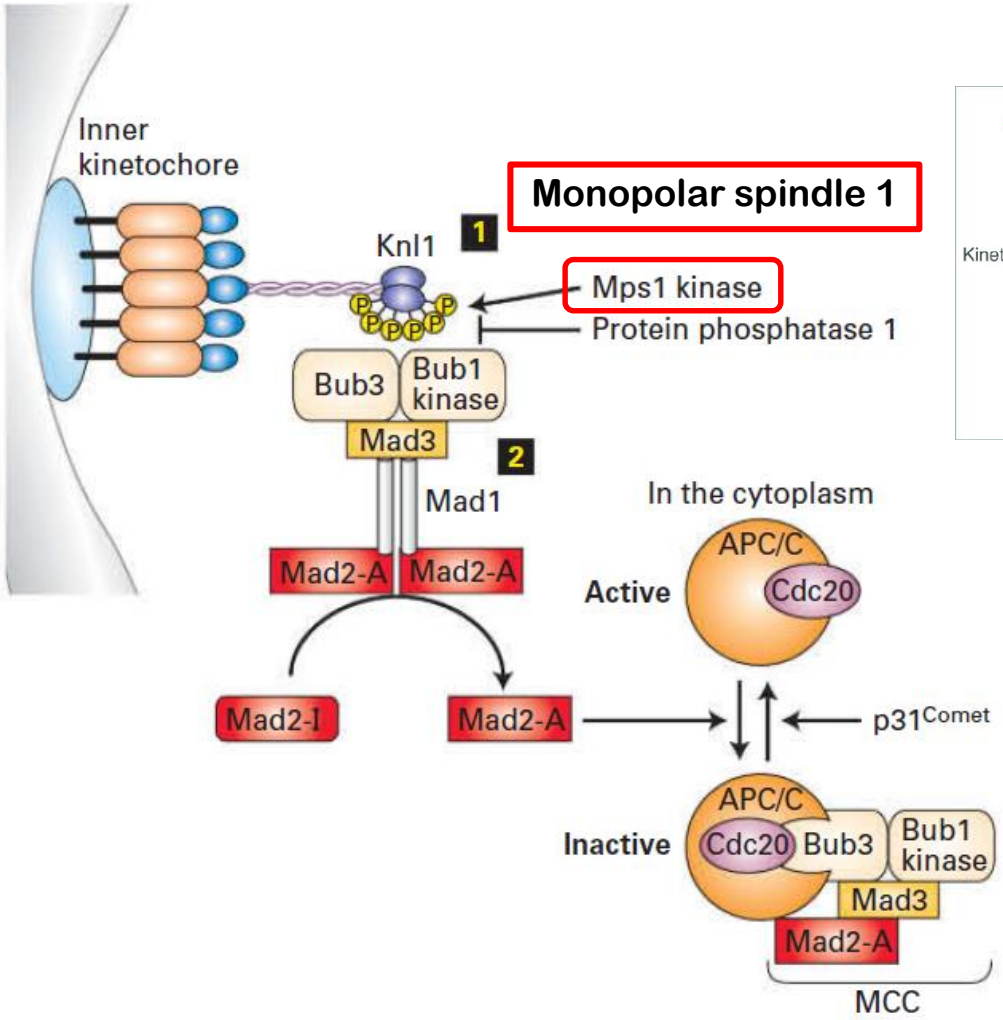
- Regulates ability to proceed through the cell cycle, such as CDK or APC activity

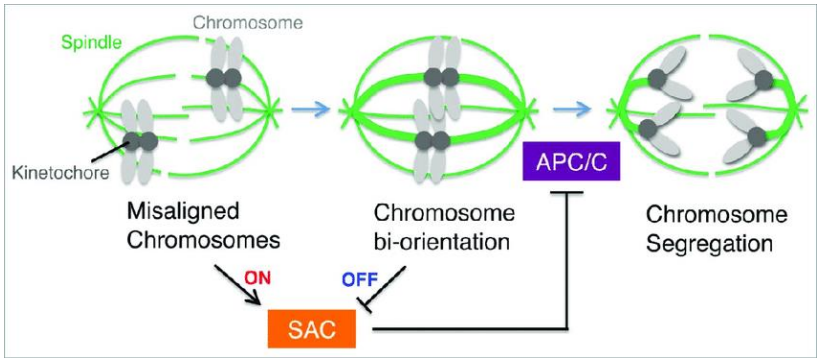
Checkpoint controls in the cell cycle



- **DNA-damage checkpoints (4a-d) occur at several steps. If damage is detected, the cell cycle is arrested and the damage repaired, if possible.**
- **Severe DNA damage may trigger apoptosis.**

Spindle Assembly Checkpoint (SAC)

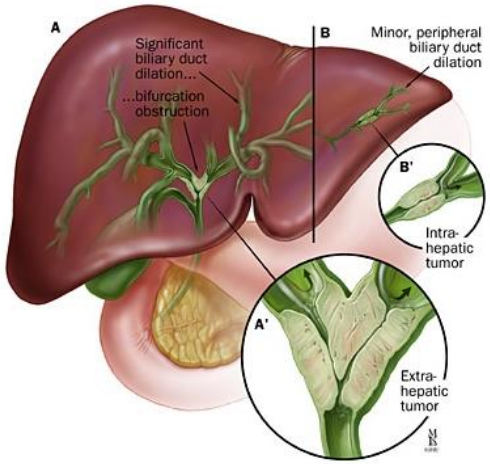




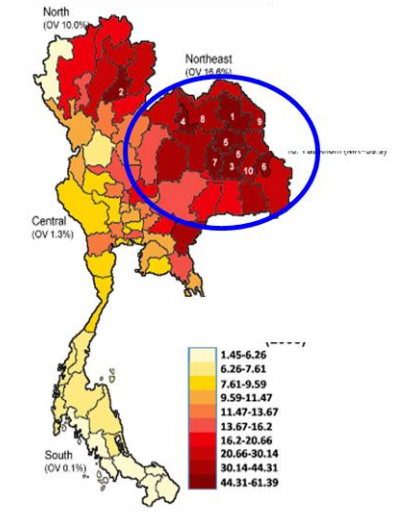
DOI:10.1080/15384101.2015.1128596

Prevents Chromosome Segregation Until Chromosomes Are Accurately Attached to the Mitotic Spindle

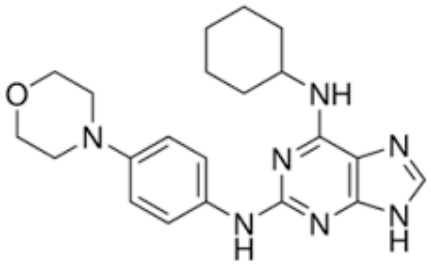
Cancer is a failure of cell division control (uncontrolled cell growth).



Cholangiocarcinoma (CCA) or bile duct cancer



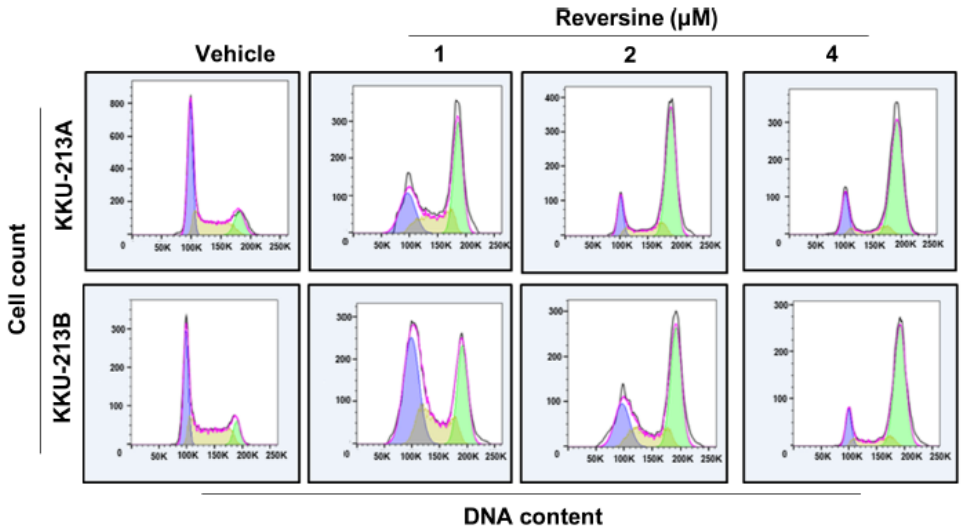
Sripa et al., Acta Trop. 2011

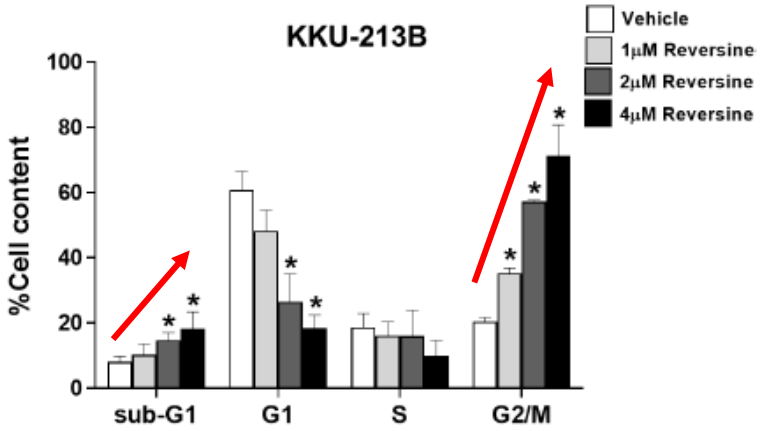


Reversine is a selective inhibitor of MPS1

Can Reversine be used for CCA treatment?

Reversine induced G2/M arrest and apoptosis





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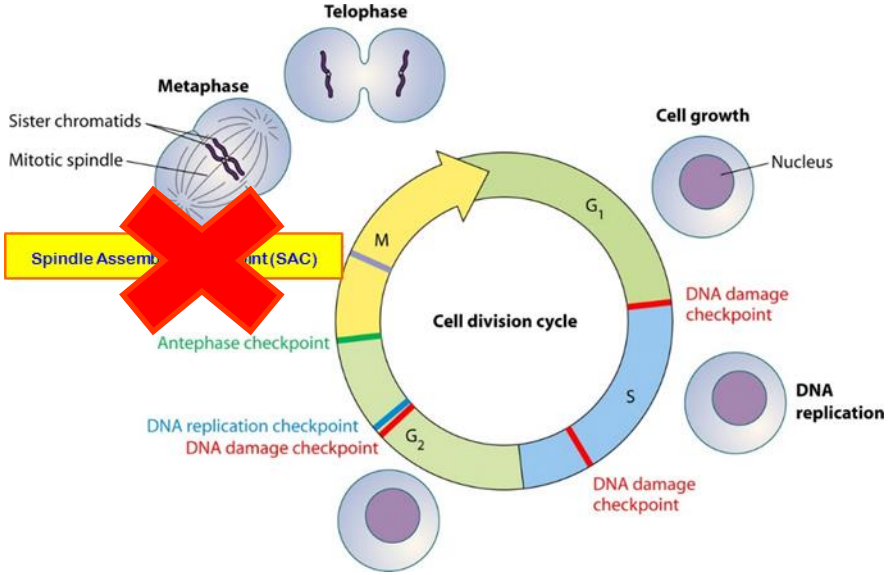
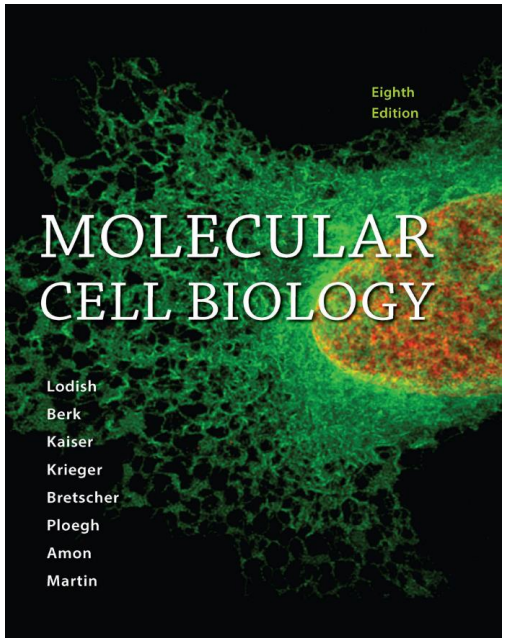


Reversine inhibited cell cycle of CCA cells

Conclusions

1. The cell cycle is a coordinated and tightly organized process to ensure the successful replication of the cell.
2. Activity of CDK-Cyclins is determined by:
    1. Synthesis of Cyclins.
    2. Reversible phosphorylation/dephosphorylation of stimulatory and inhibitory sites on CDK.
    3. Ubiquitin mediated degradation of Cyclins.
    4. CDK inhibitors – INK4 and CIP/KIP families.
3. Checkpoints can stop the cell cycle if all steps have not been properly completed.
4. Cancers have many alterations in cell cycle proteins and their selective inhibitors are now used in cancer treatment.

References



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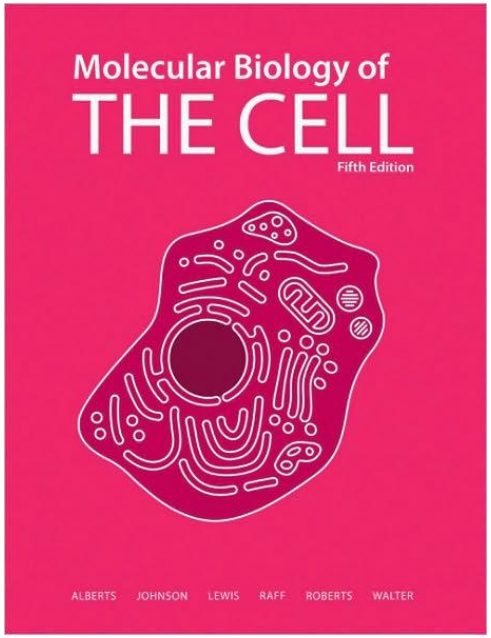

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