CELL CYCLE

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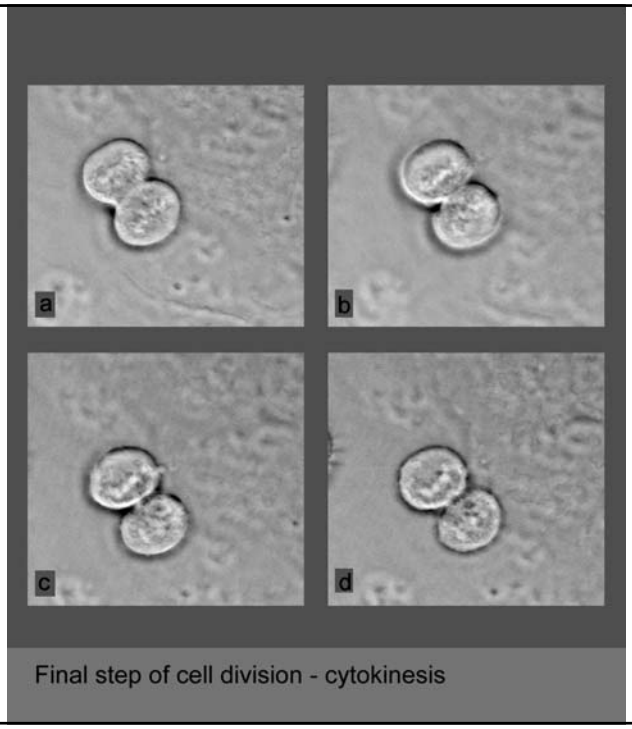


Final step of cell division - cytokinesis

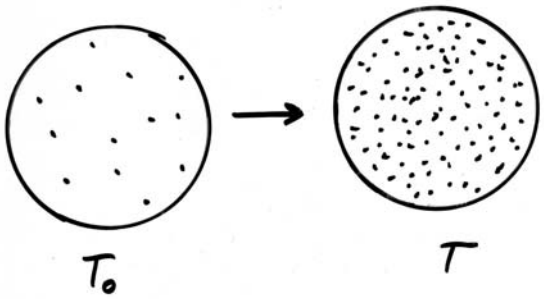
Cells in culture

doubling time ... the time interval in which the cell number doubles

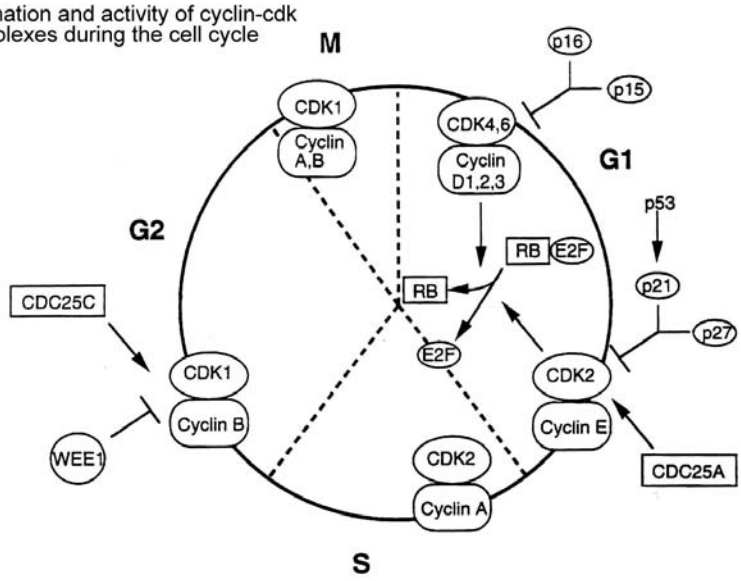
number of doublings = log N/No x 3.33

No...number of cells at time To

N....number of cells at time T



Formation and activity of cyclin-cdk complexes during the cell cycle



Summary of the regulation of cyclin/cdk complexes during cell cycle

Cell cycle phase	Cyclin-cdk complex	inhibitor	activation	Substrate(s)
G1	**Cyclin D/cdk 4,6**	p16 family, p21 family	CAK, Cdc25A	Rb protein
G1/S	**Cyclin E/cdk 2**	p21 family	CAK, Cdc25A	Rb protein, NPAT, cdc6
S	**Cyclin A/cdk 2** (Cyclin A/cdk 1)	p21 family	CAK, Cdc25	Rb protein, pre-RC, E2F
G2/M	**Cyclin B/cdk 1** (Cyclin A/cdk 1)	p21 family	CAK, Cdc25C	Several substrates required for mitosis (APC, lamins, condensins,..)

Summary of cell cycle regulation

Basic terminology:

Cyclins – conserved proteins with homologous regions; their cellular levels profoundly oscillate during the cell cycle due to transcriptional regulation and different degradation of the protein.
Cyclins are catalytic subunits of active cyclin-cdk complexes,
CYCLINS A, B, D(1,2,3), E

Cyclin-dependent kinases (cdks) – kinases that require a catalytic subunit (cyclin) and their activity is regulated by phosphorylation/dephosphorylation and by cdk-inhibitors.

CDK 1,2,3,4,6,7

Substrates of cyclin-cdk complexes – the most important is the retinoblastoma protein (Rb).
Rb gene family: Rb, p107, p130.

Cdk inhibitors – bind and inactivate cyclin-cdk complexes

E2F transcription factors – heterodimers of E2Fs (1-5) and DPs (1,2) activate transcription of several genes important for the S-phase. Transcription by E2F is repressed by Rb protein. Only hypophosphorylated Rb protein is capable of repressing transcription. Upon phosphorylation, Rb protein becomes inactive.

E2F targets are promoters of: DNA polymerase α, dihydrofolate-reductase, thimidine kinase, Cyclin E, cyclin A, c-myc, E2F-1 (positive loop)

Cdk inhibitors

INK4 family:
p16 (INK4a), p15 (INK4b) p18 (INK4c)

Inhibit only cyclin D/cdk 4,6 complexes

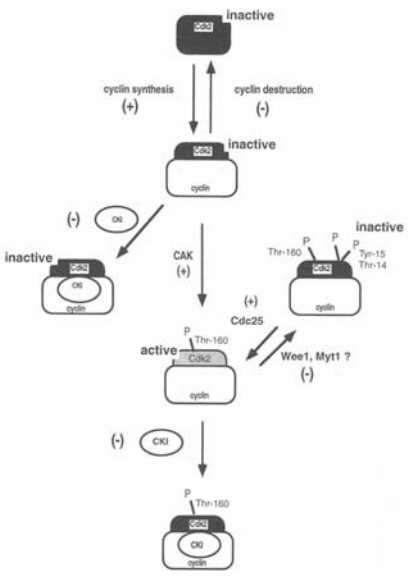
p21 (Cip1) family

p21 (Cip1, WAF1), p27 (kip1), p57 (Kip2)

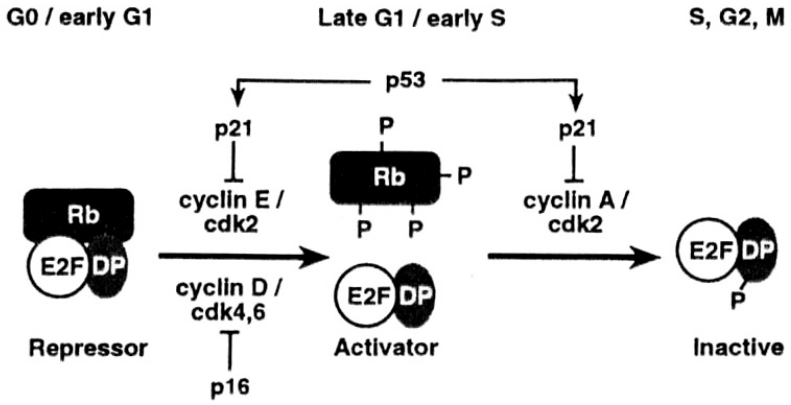
Inhibit both cyclin D/cdk 4,6 complexes nad cyclin E/cdk2 and cyclin A/cdk2 complexes

p14ARF (p19ARF in mouse)
stabilizes the p53 protein

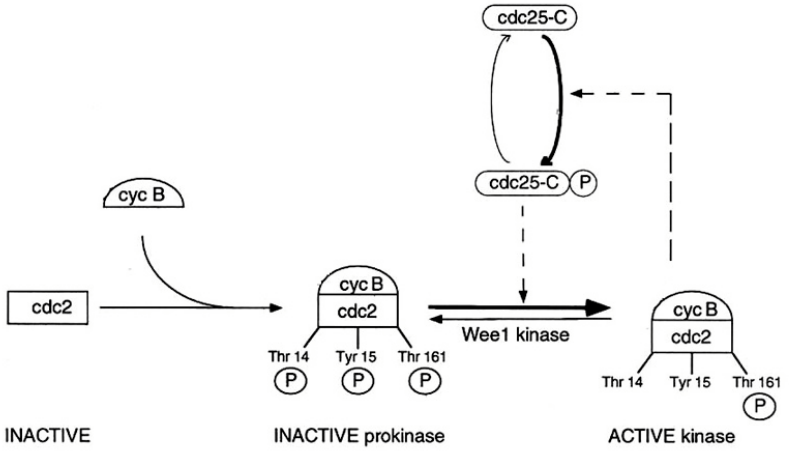
Activation/inactivation of cdk2



ACTIVATION OF E2F/DP TRANSCRIPTIONAL ACTIVITY BY PHOSPHORYLATION OF Rb PROTEIN



Activation of cdk1 (=cdc2) by phosphorylation/dephosphorylation



Cell cycle checkpoints

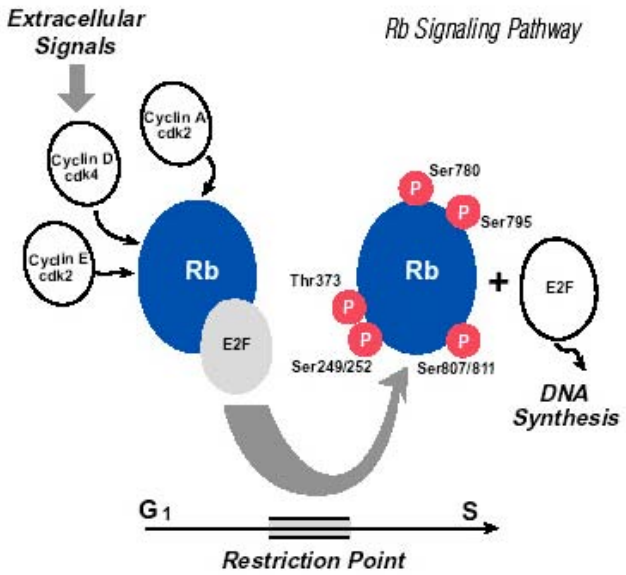
Checkpoints enable cells to halt the cell cycle and repair damaged DNA or complete spindle assembly at mitosis:

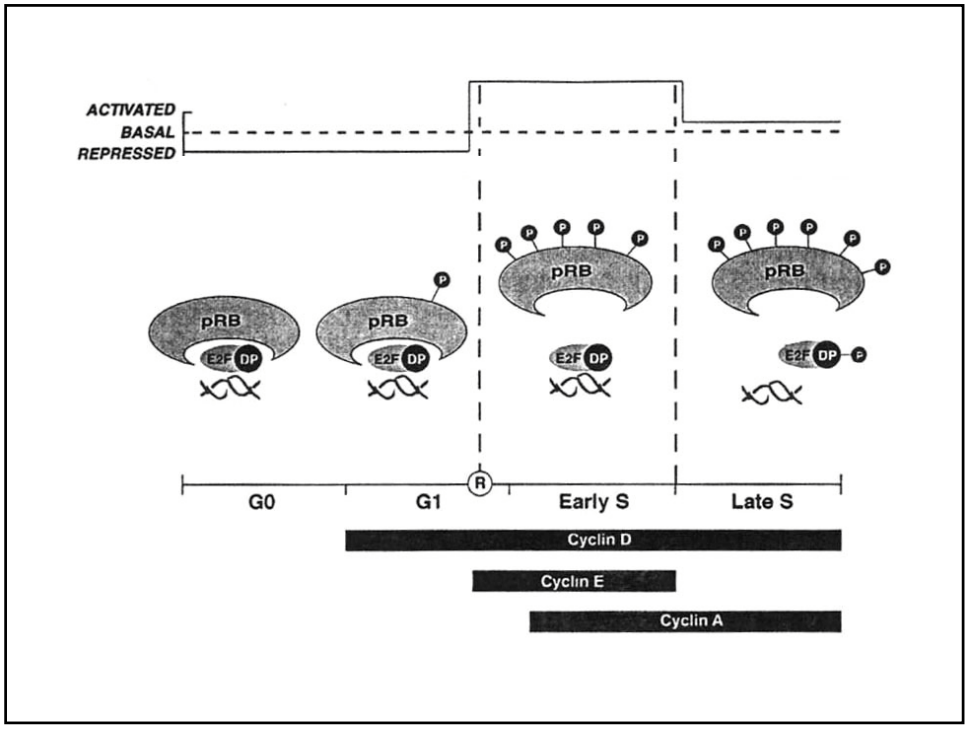
- restriction point
  after this point, the cell is committed to enter the S-phase

- DNA replication checkpoint
  this checkpoint ensures that mitosis occurs only after DNA has replicated completely (DNA replicates once and only once during a single cell cycle)

- spindle assembly checkpoint
  ensures proper segregation of chromosomes during mitosis (at the metaphase to anaphase transition)

- DNA damage checkpoint(s)
  cell cycle can be arrested in G1, S , or G2




ACTIVATED
BASAL
REPRESSED
pRB
E2F
DP
G0
G1
R
Early S
Late S
Cyclin D
Cyclin E
Cyclin A