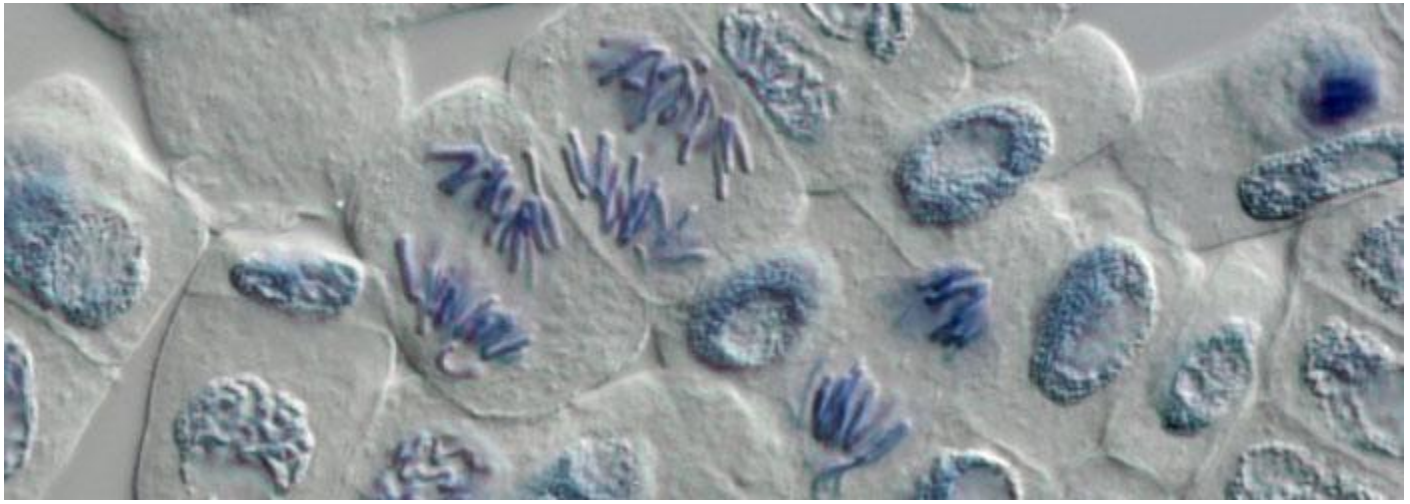
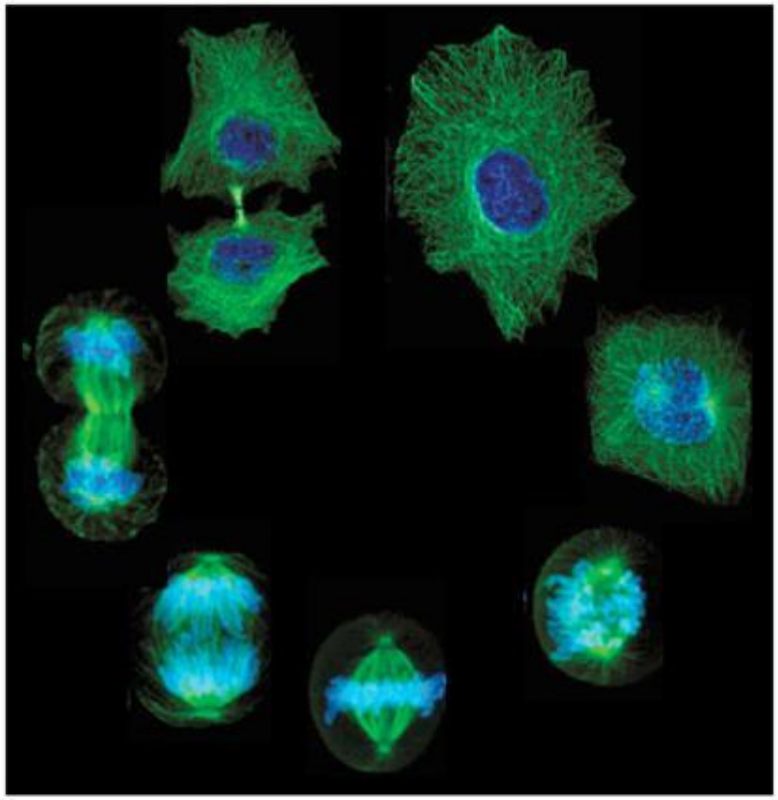
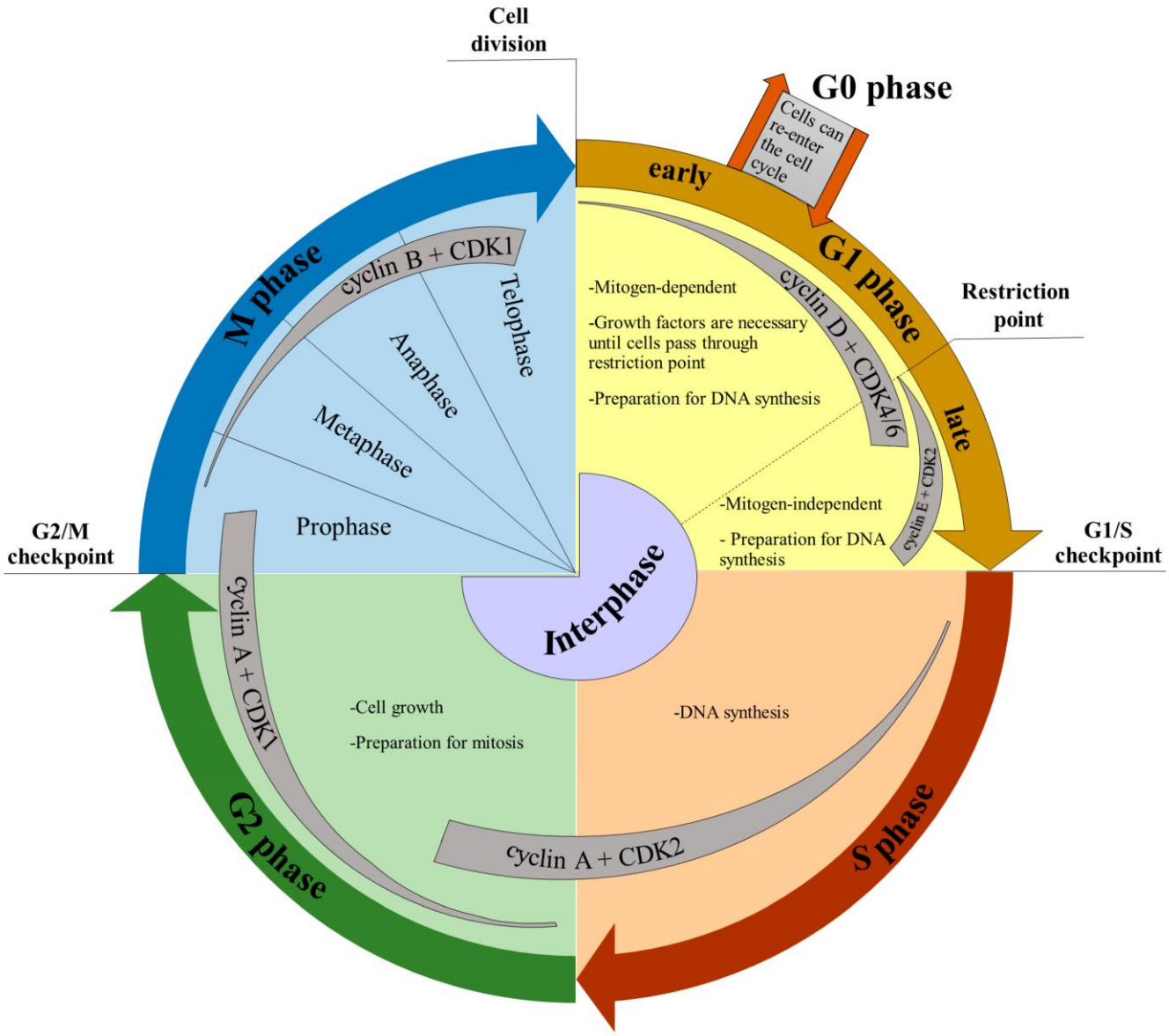


Cell cycle regulation

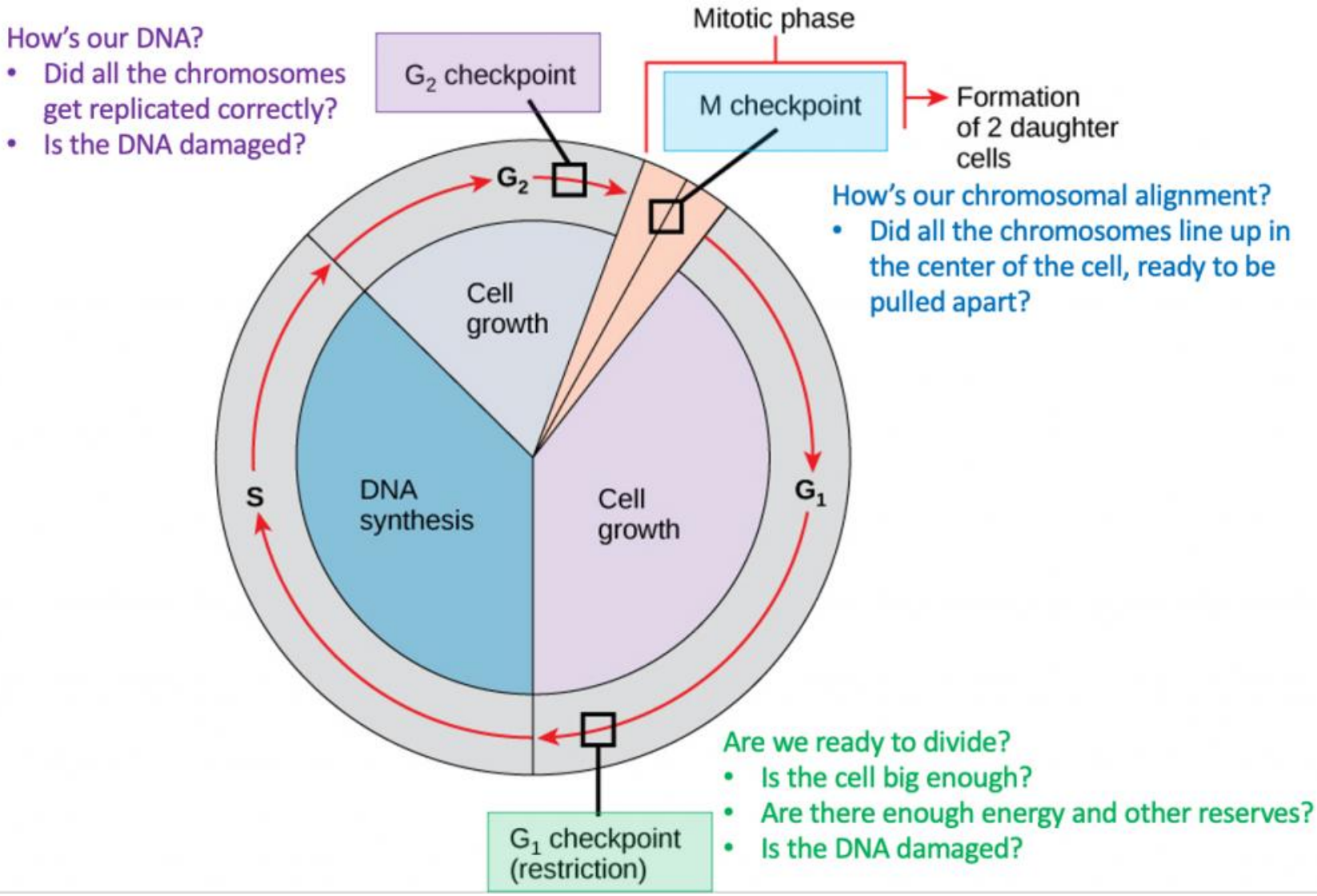
Cell cycle is a process which includes many different events – all finally leading to cell division.



Cell cycle phases

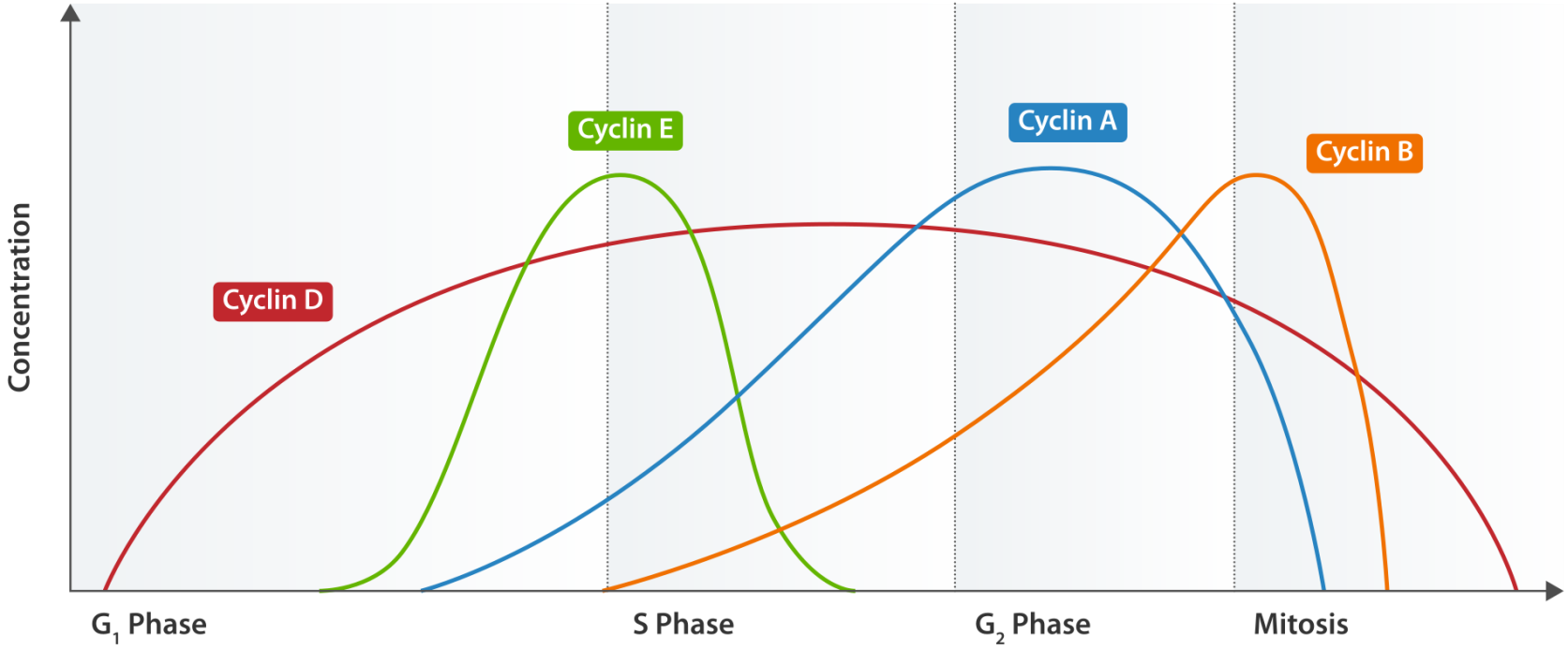


Cycle checkpoints

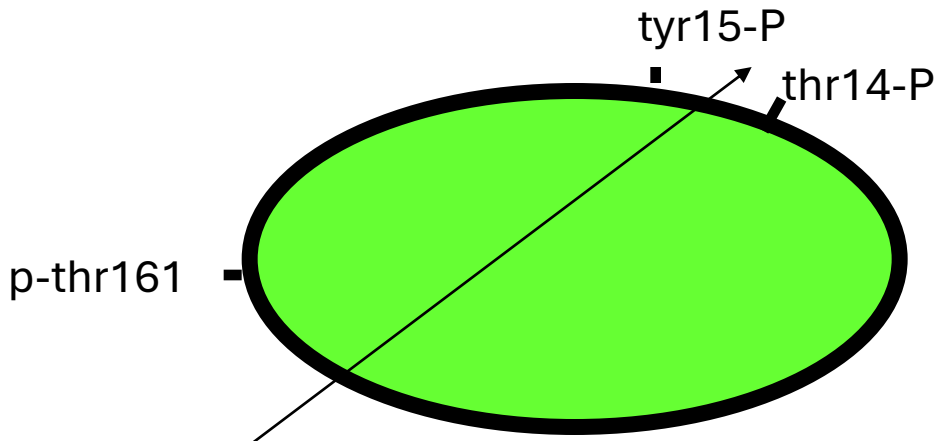


Cell cycle control

- 2001 r. Nobel prize for Leland Hartwell, Paul Nurse and Timothy Hunt

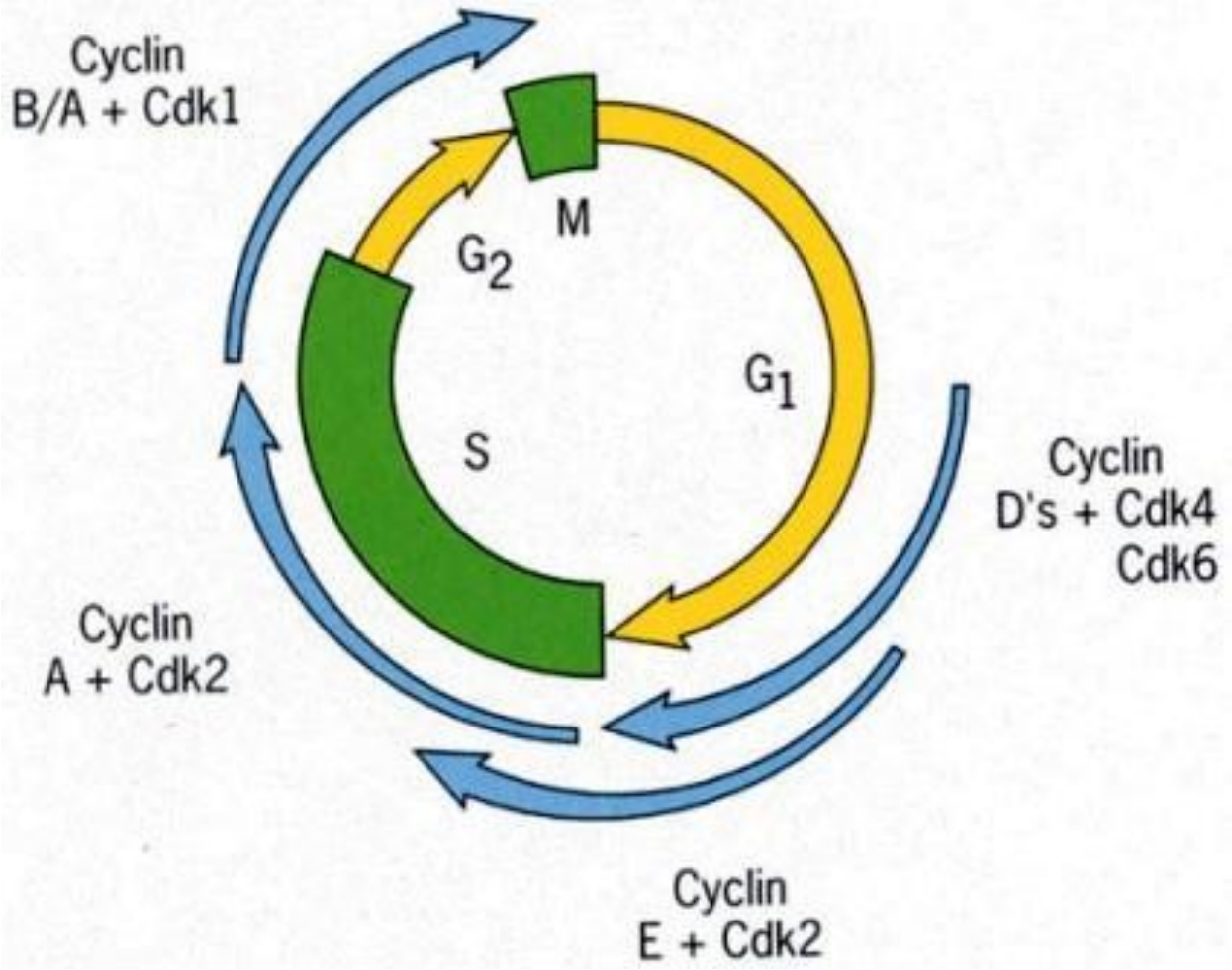


Cyclin dependent kinases (Cdk)

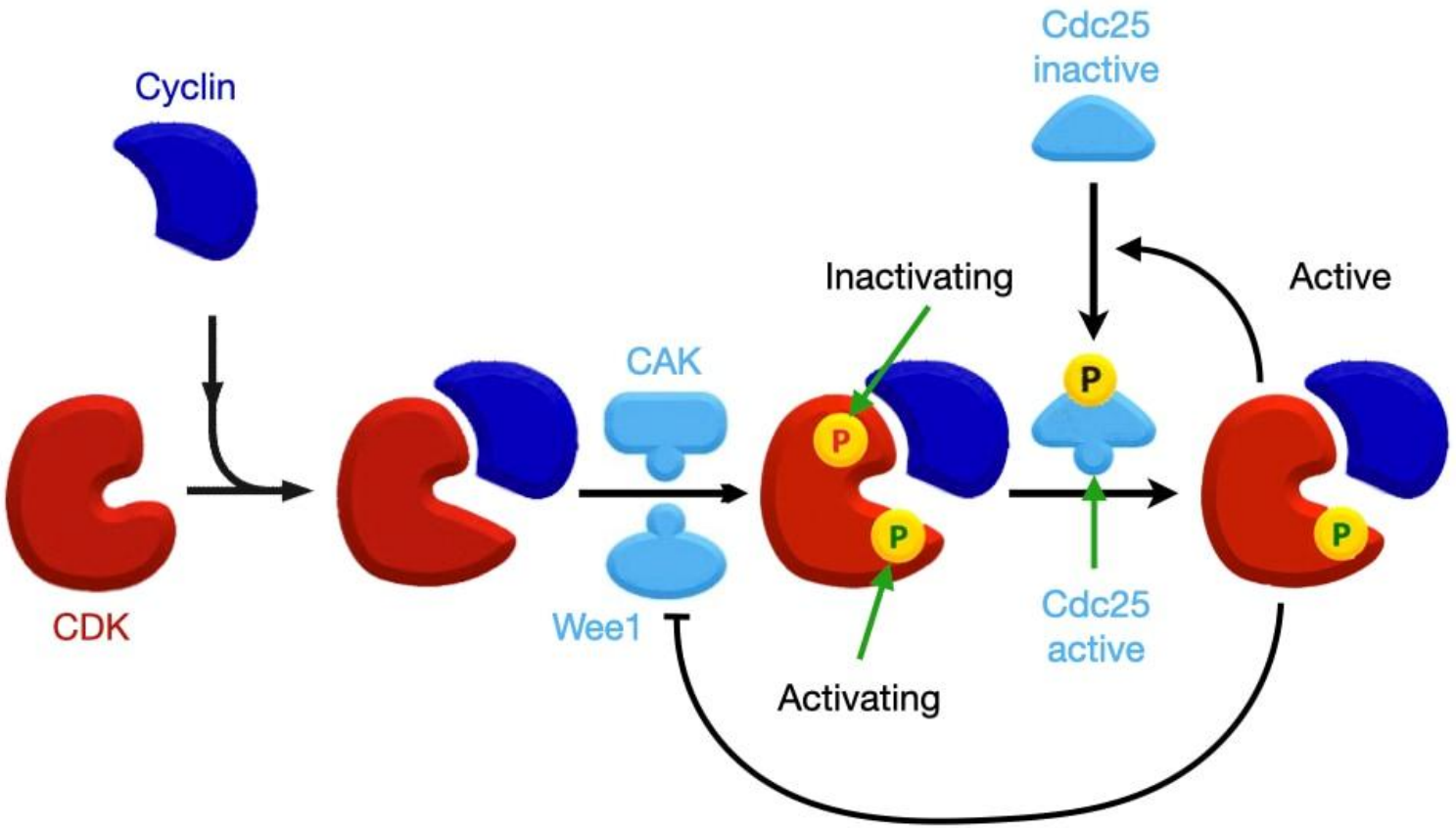


- Protein kinases
- Bind cyclins
- Have kinase and regulatory domains
- **Their concentration is constant through all the cycle**

Cell cycle regulation – cyclins and kinases complexes



Kinase activation



Kinase deactivation through cyclin degradation in proteasome

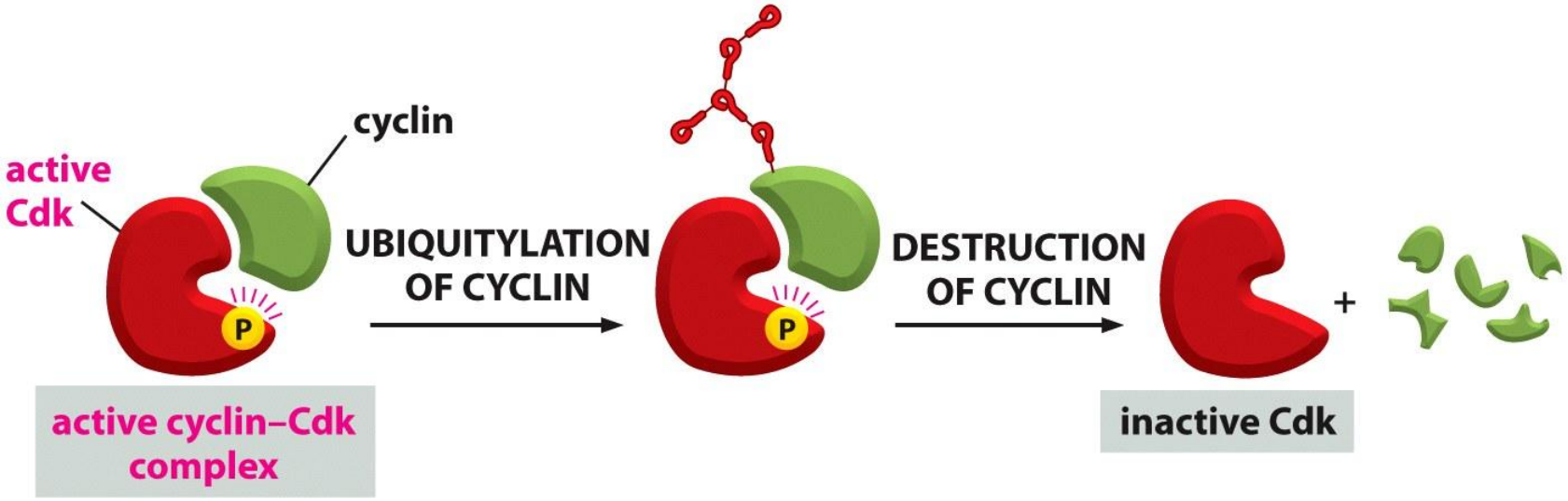
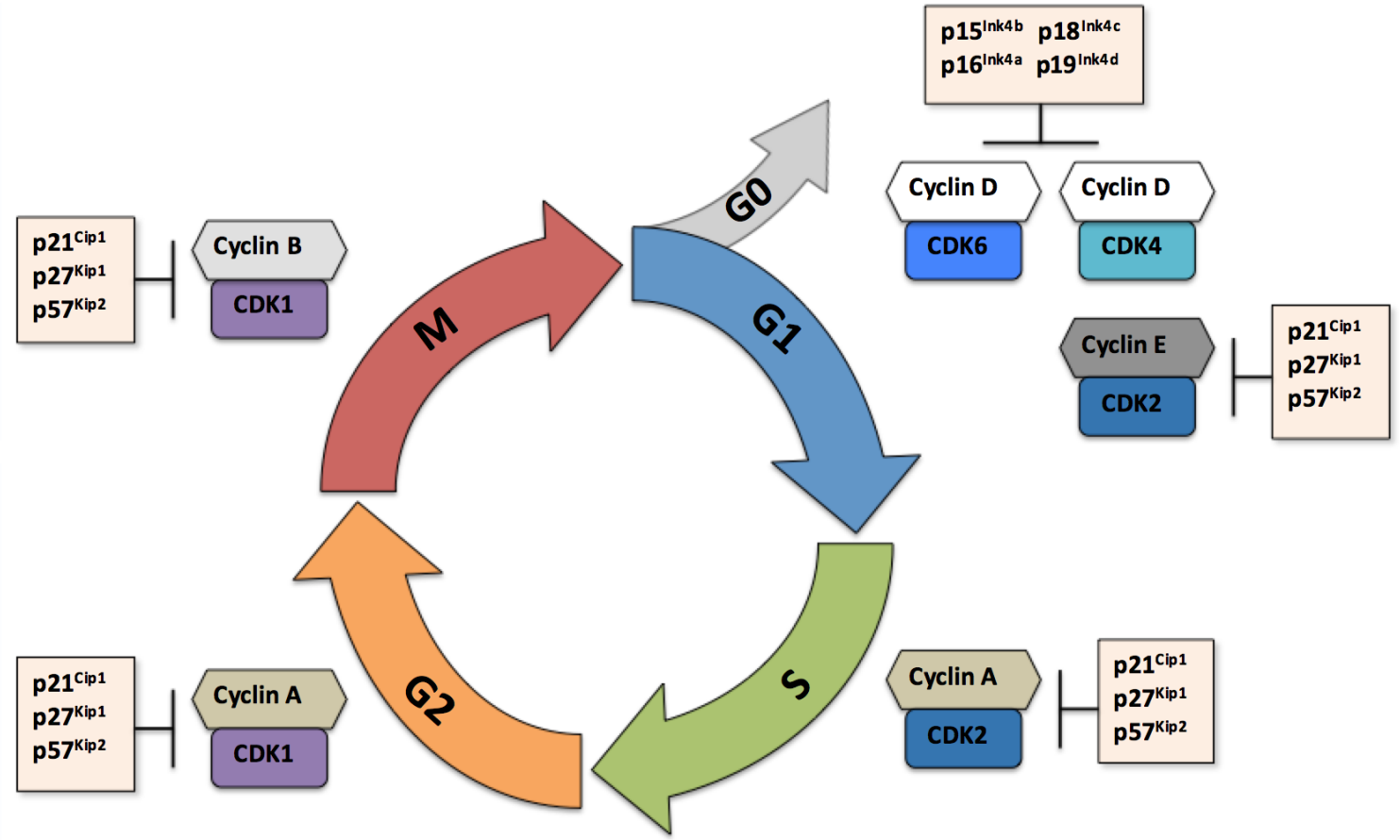


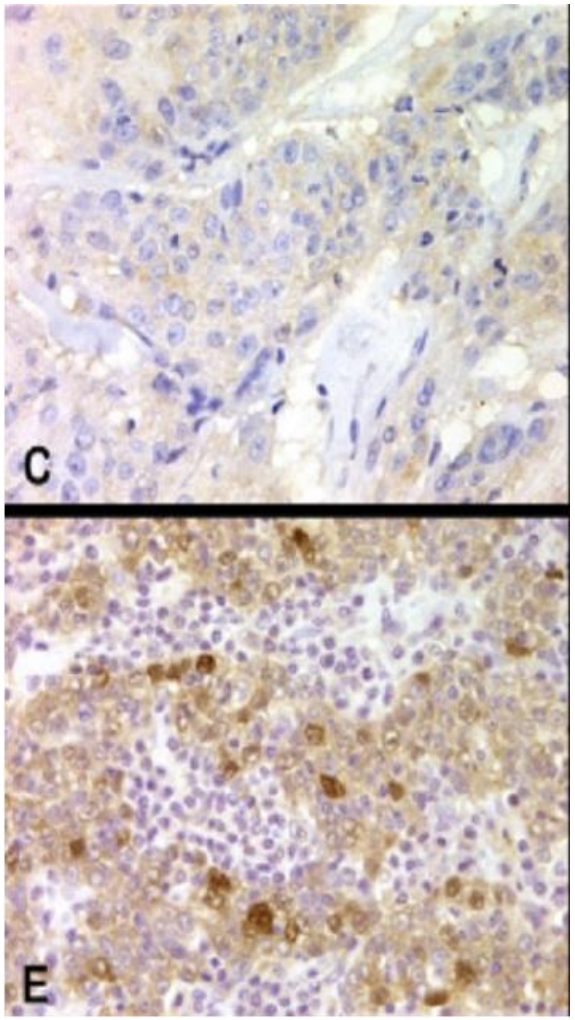
Figure 18-11 Essential Cell Biology 3/e (© Garland Science 2010)

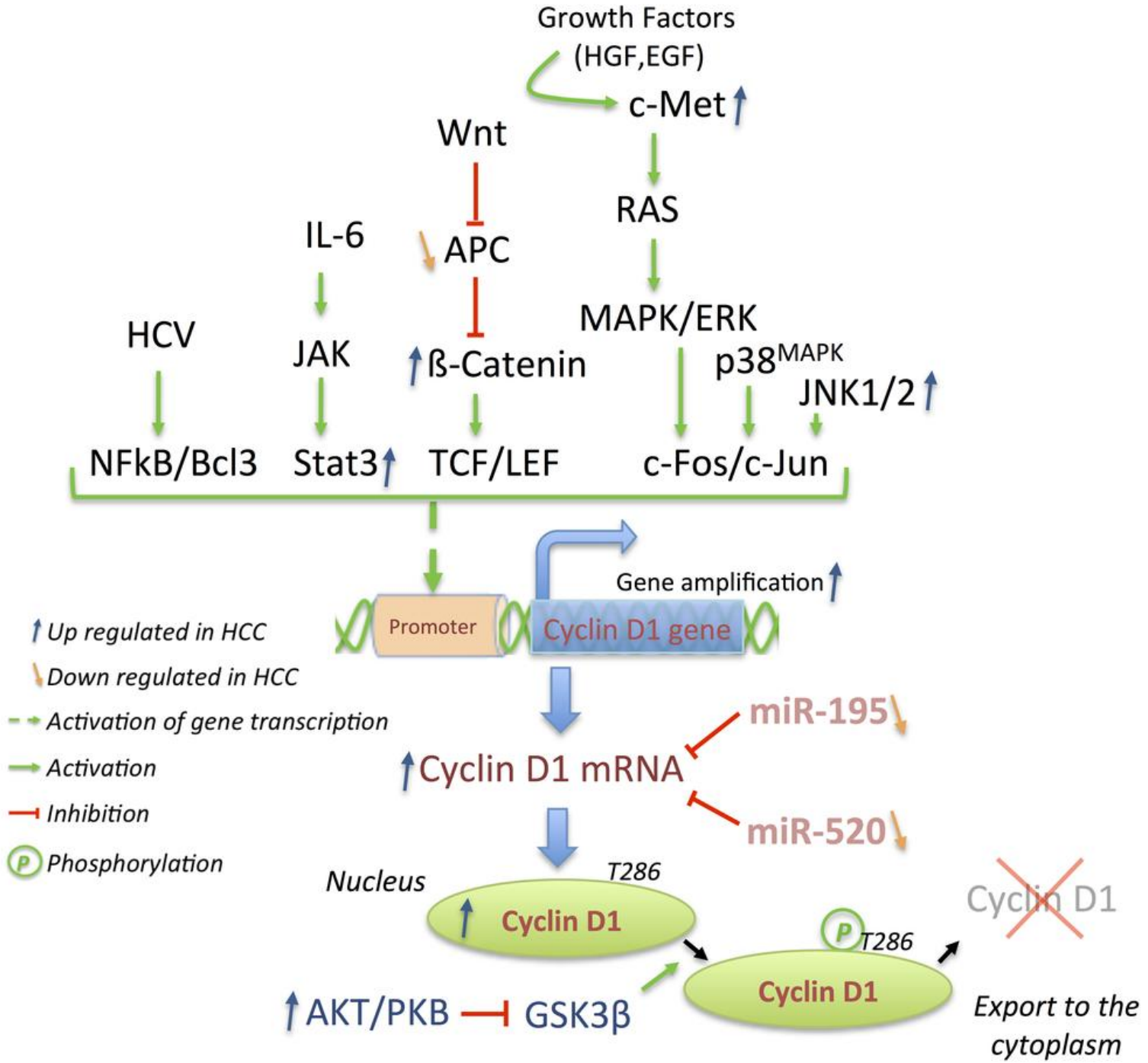
Kinase inhibitors



Phase G1 – cyclin D

- Cyclin D is unique because it needs mitogen stimulation to be produced
- High cyclin D expression is characteristic for tumors




Growth Factors
(HGF,EGF)
c-Met
Wnt
RAS
IL-6
APC
HCV
JAK
MAPK/ERK
ß-Catenin
p38MAPK
JNK1/2
NFkB/Bcl3
Stat3
TCF/LEF
c-Fos/c-Jun
Gene amplification
Promoter
Cyclin D1 gene
Up regulated in HCC
Down regulated in HCC
Activation of gene transcription
Activation
Inhibition
Phosphorylation
miR-195
Cyclin D1 mRNA
miR-520
Nucleus
T286
Cyclin D1
Cyclin D1
T286
Cyclin D1
AKT/PKB
GSK3β
Export to the
cytoplasm

Cyclin D and Rb protein

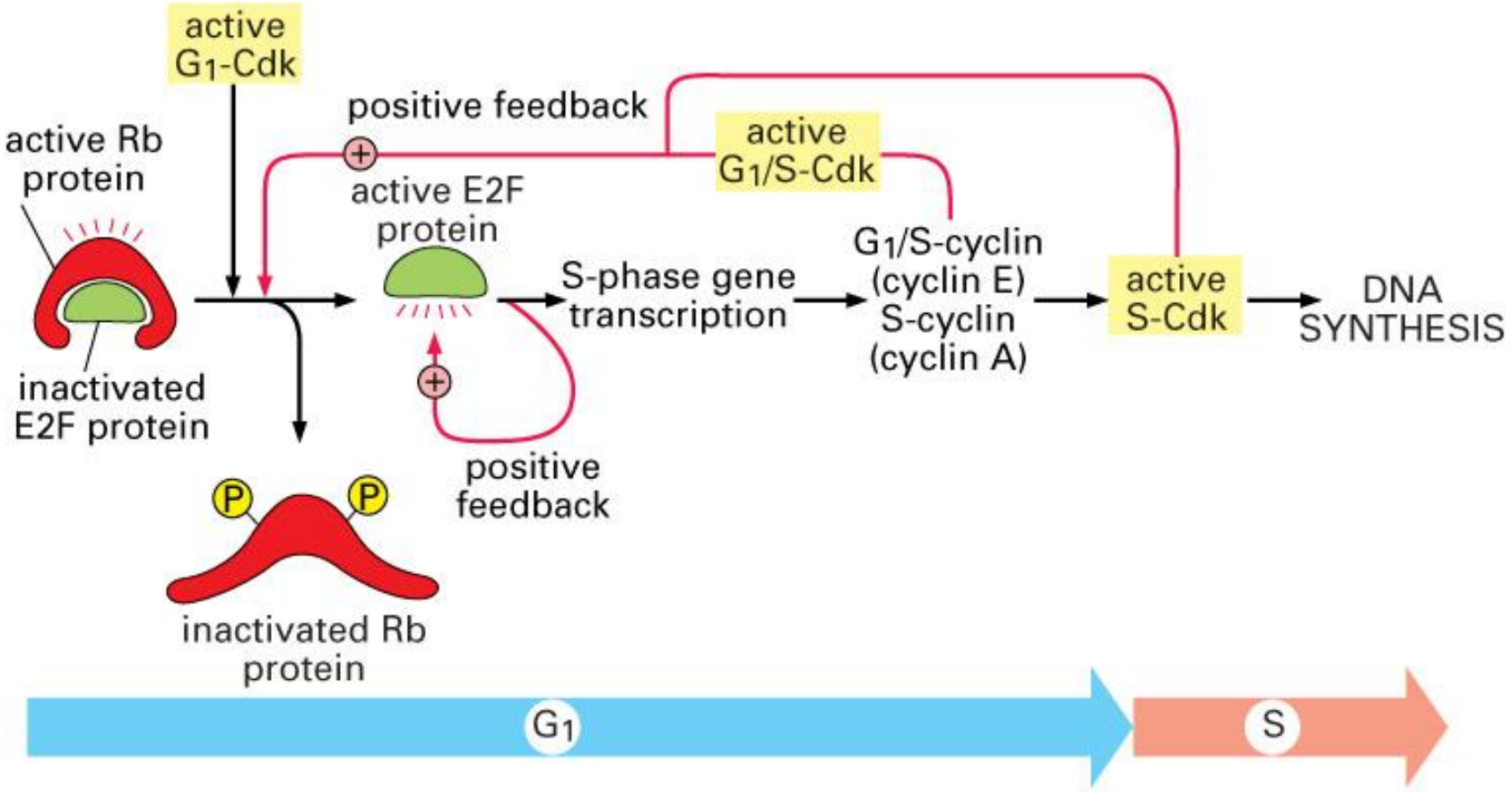


Figure 17–30. Molecular Biology of the Cell, 4th Edition.

Rb protein and p16 inhibitor

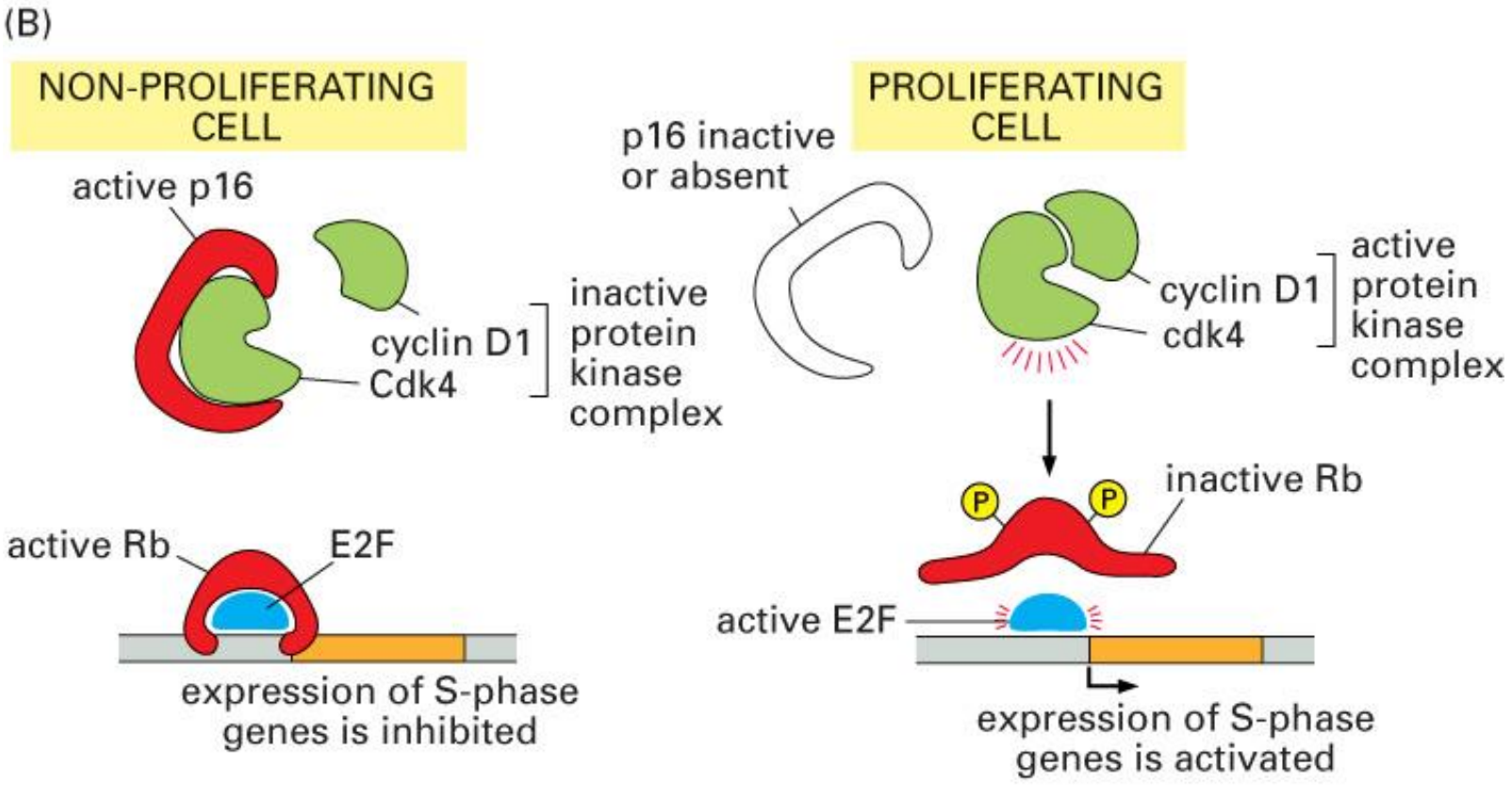
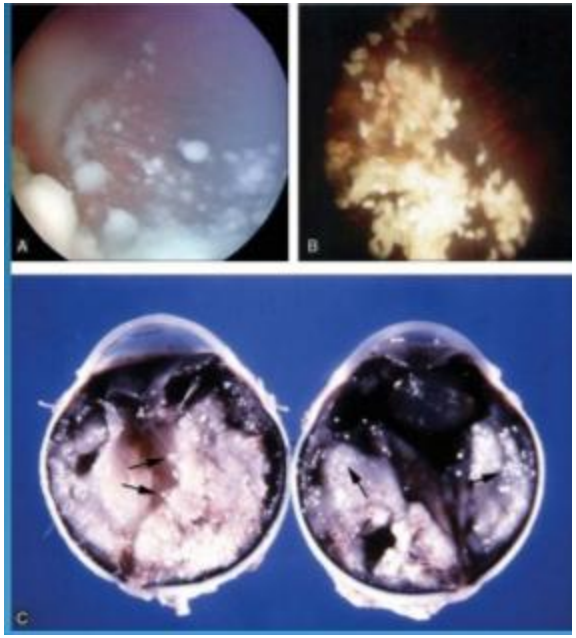
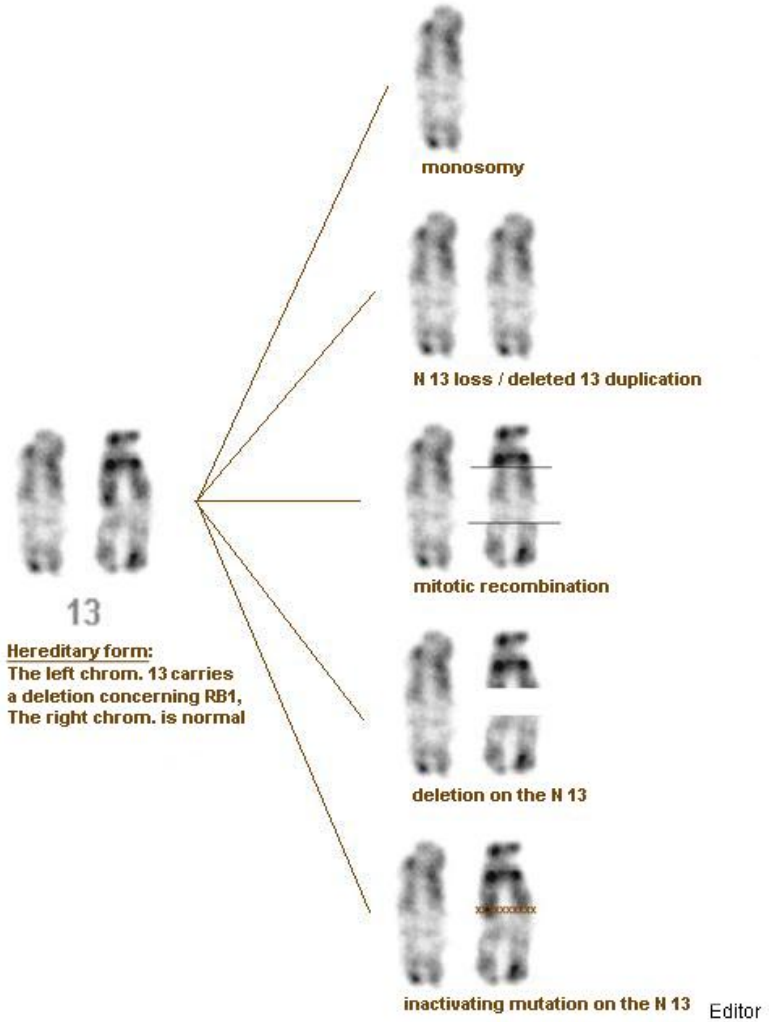


Figure 23–32 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

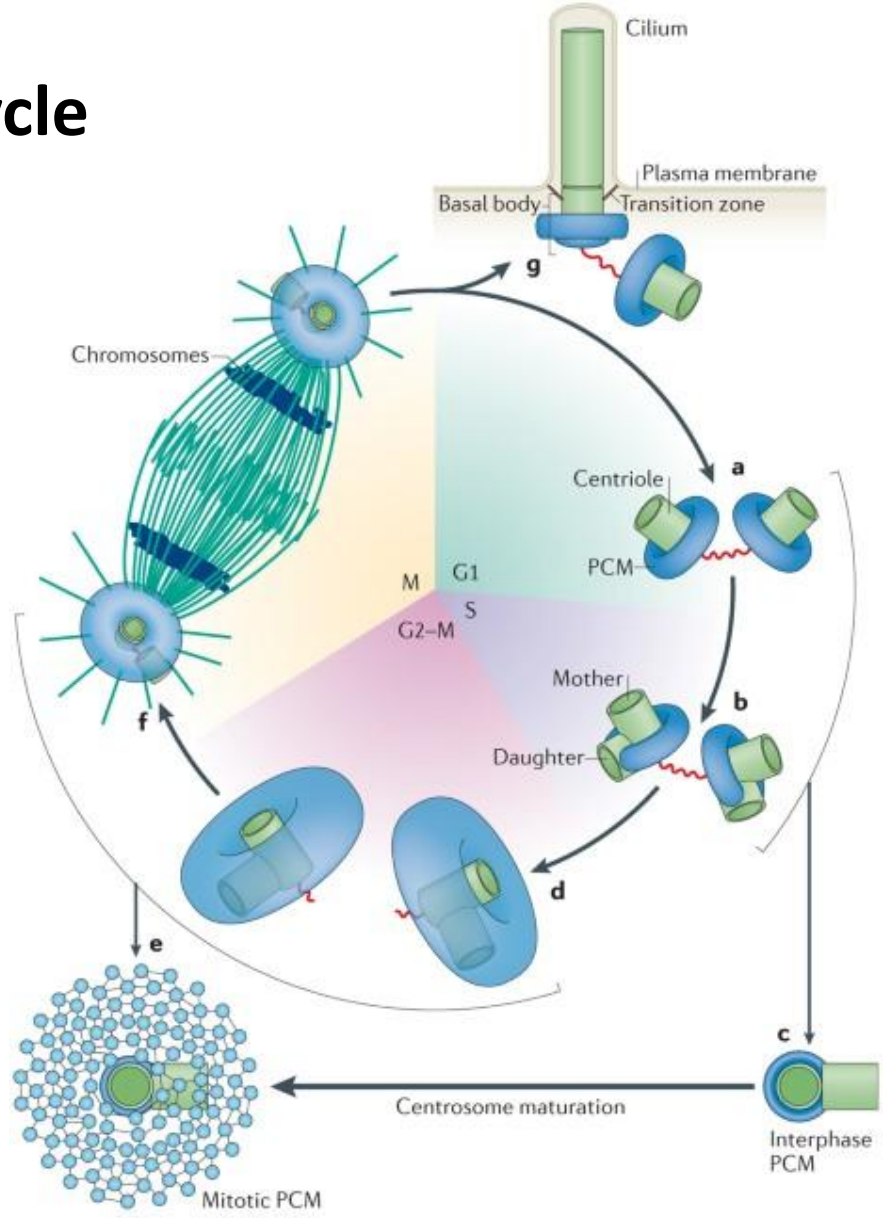
Retinoblastoma





Editor

Centrosome cycle



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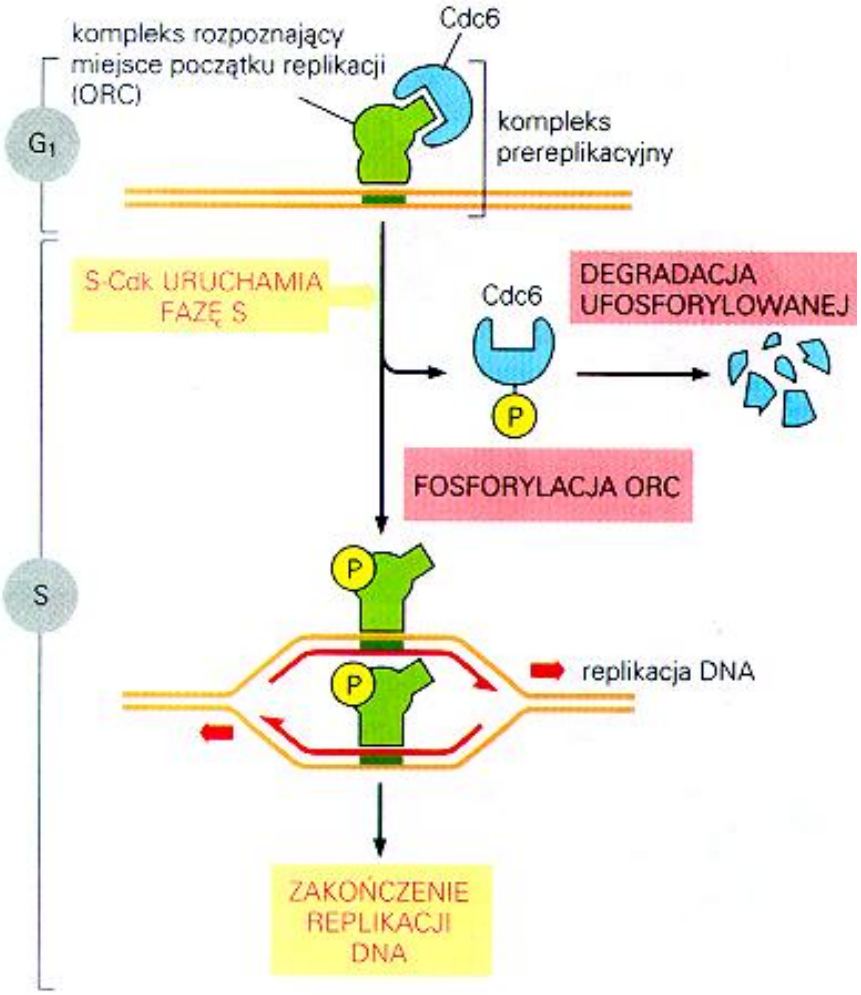
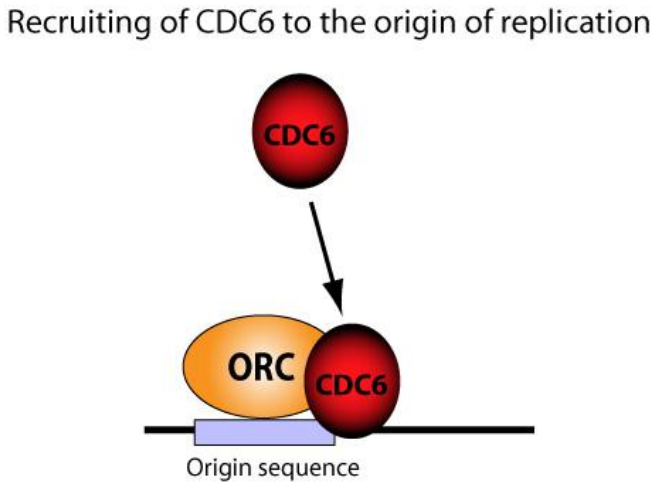
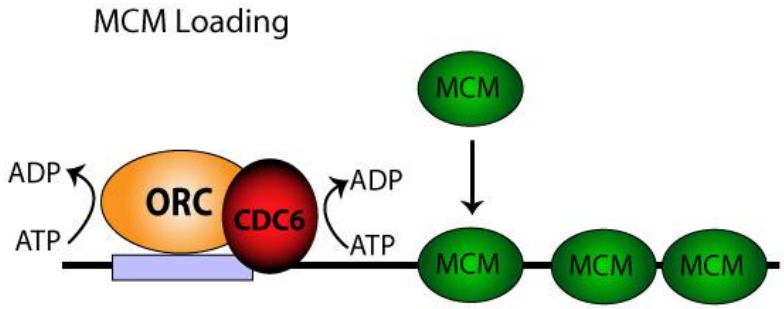
Replication control – cyclin A and CDK2







DNA damage – p53 protein

- Short life span (10-15 minutes)
- Binds MDM2 and is degraded in proteasome
- When DNA is damaged p53 is phosphorylated
- P53 accumulates in damaged cells

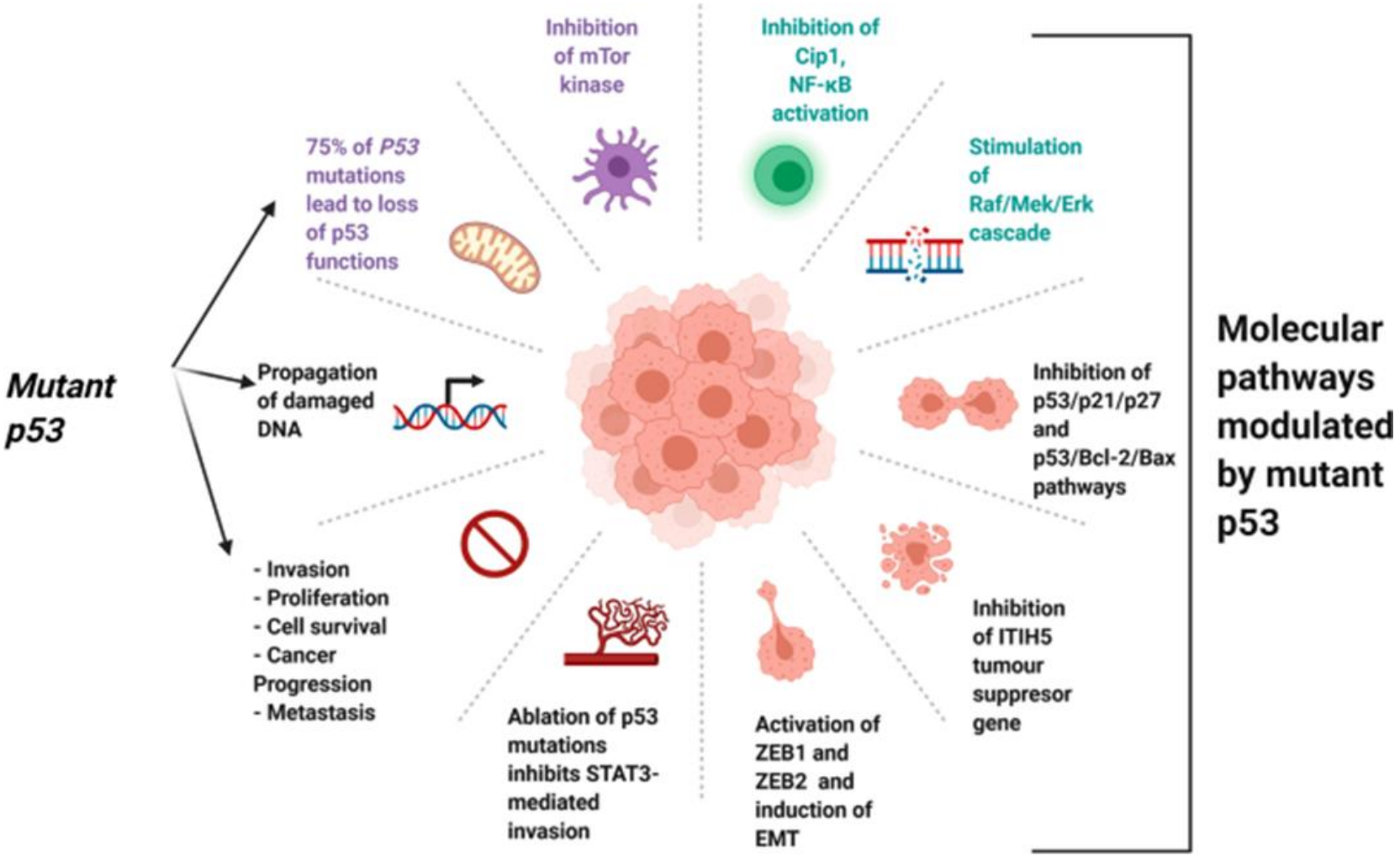
P53 is a transcription factor

p53 induces transcription of:

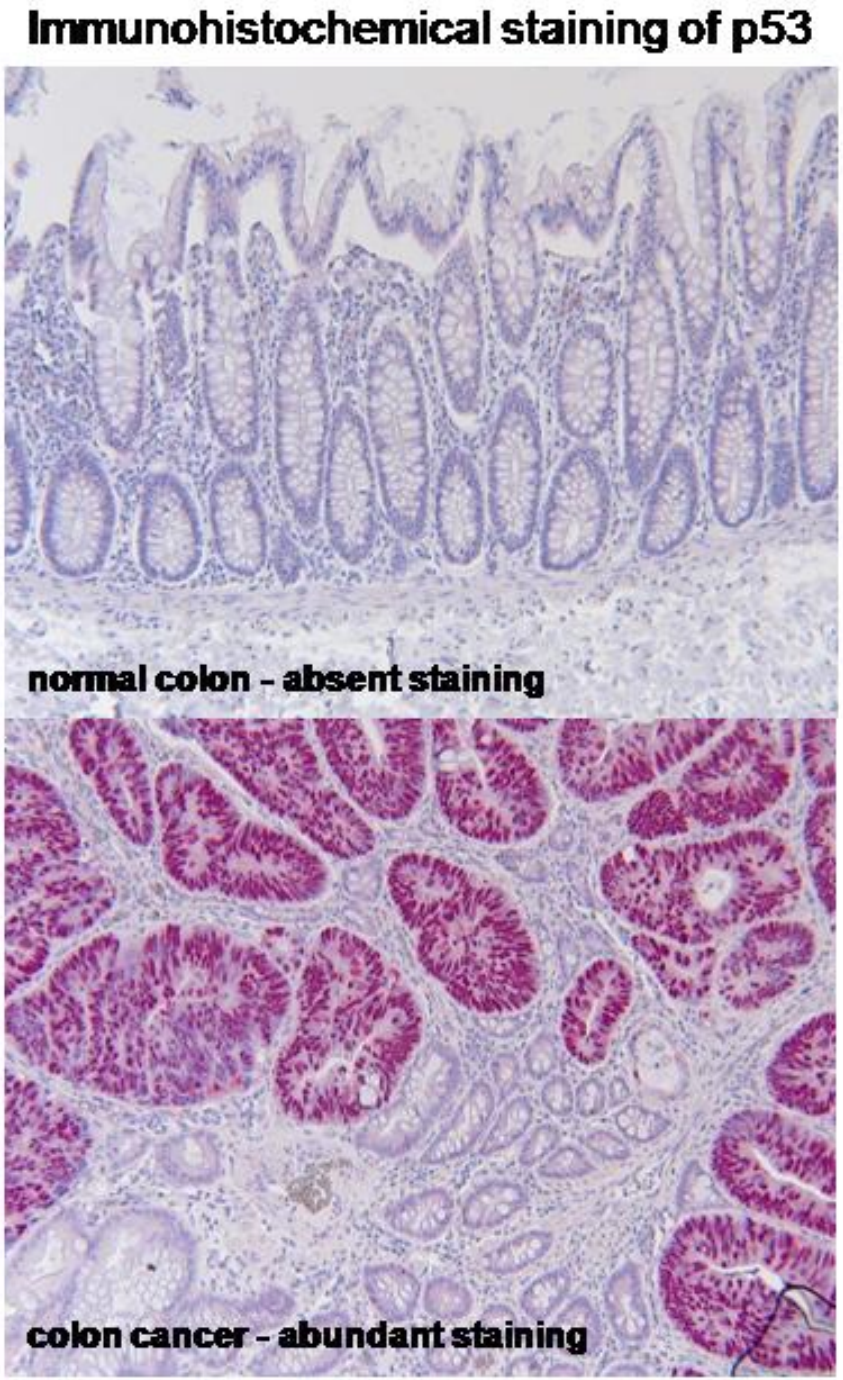
- p21 - CDK innibitor – cycle block
- BAX – apoptosis promotying protein – apoptosis
- DNA repair proteins

HOW TO CONTROL WHICH PATHWAY P53 CHOOSES?

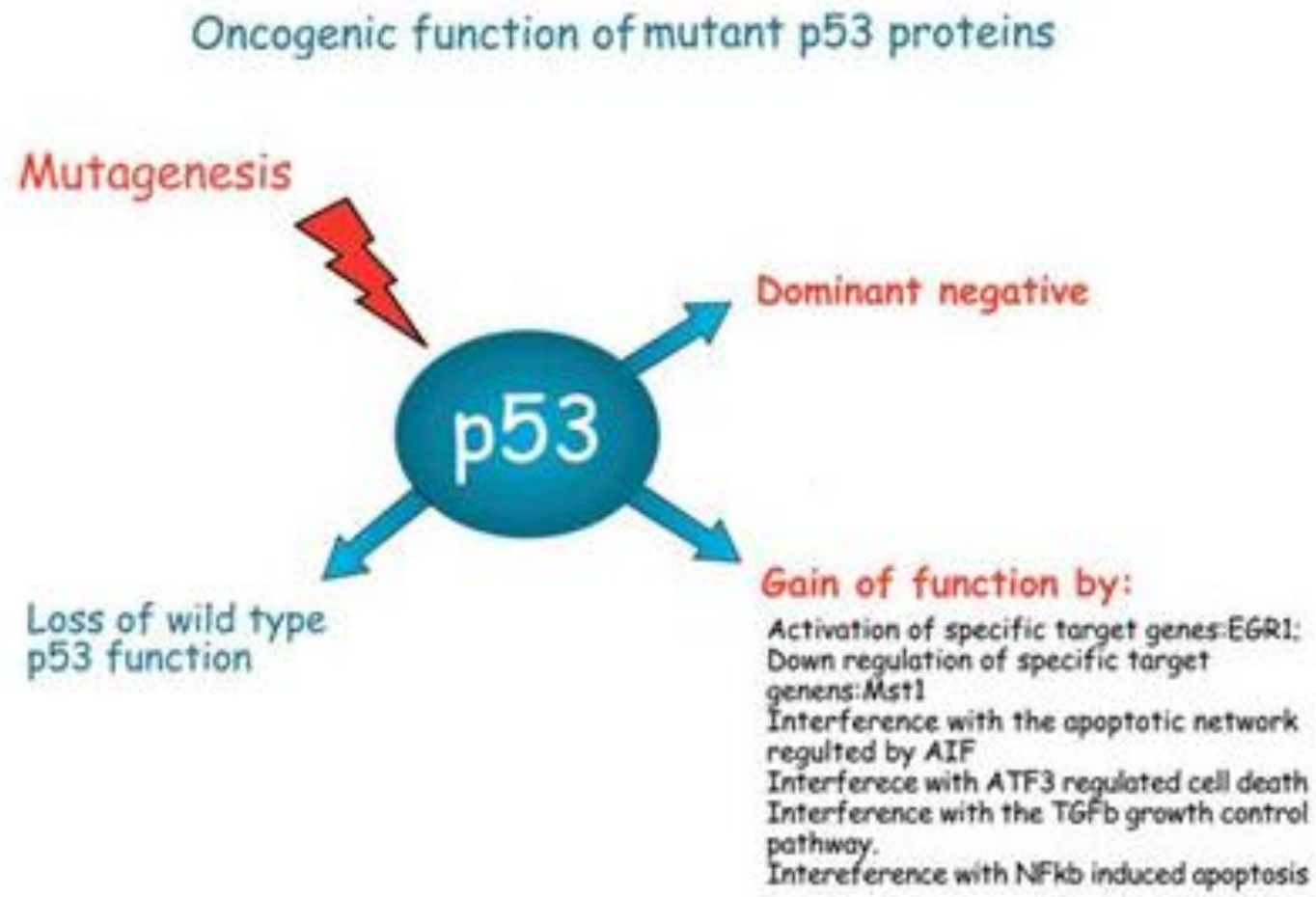
P53 and cancer



Colon cancer

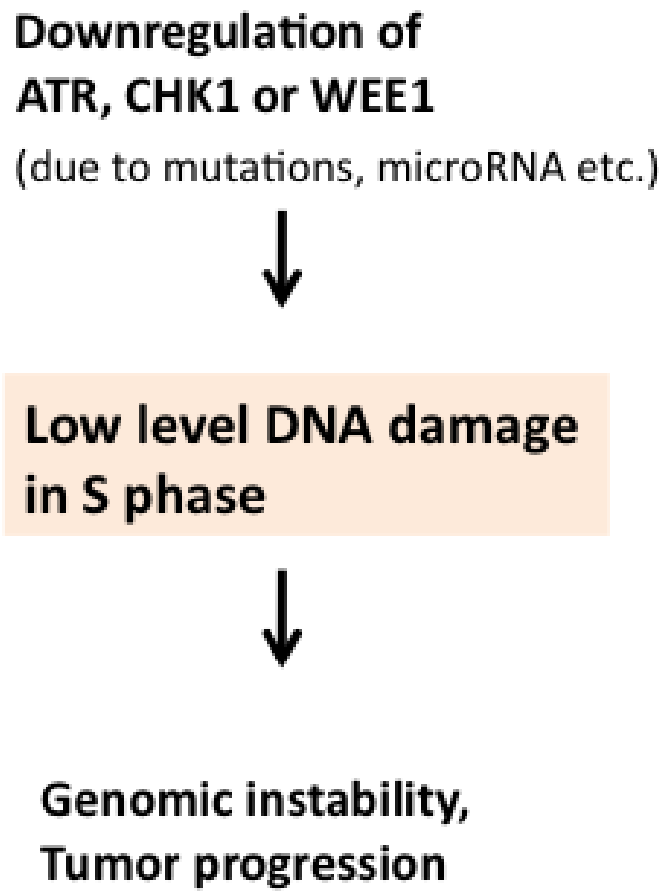


Li-Fraumeni syndrome

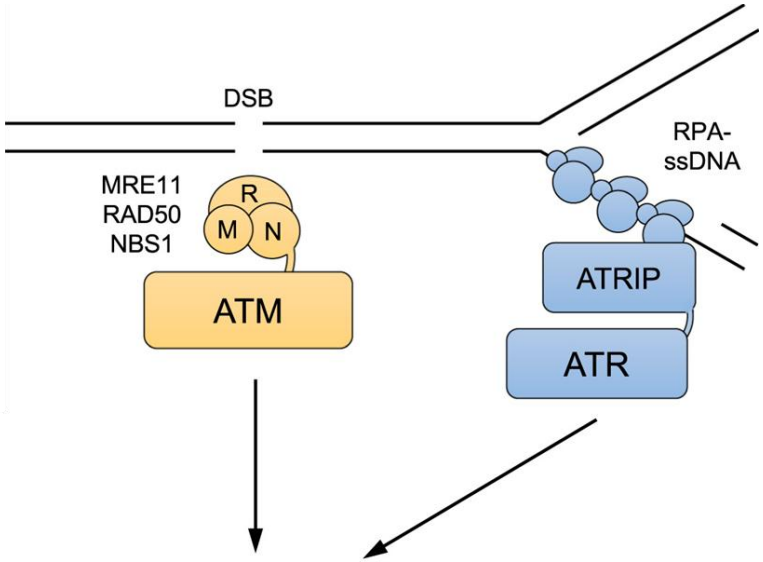


DNA repair during the cycle

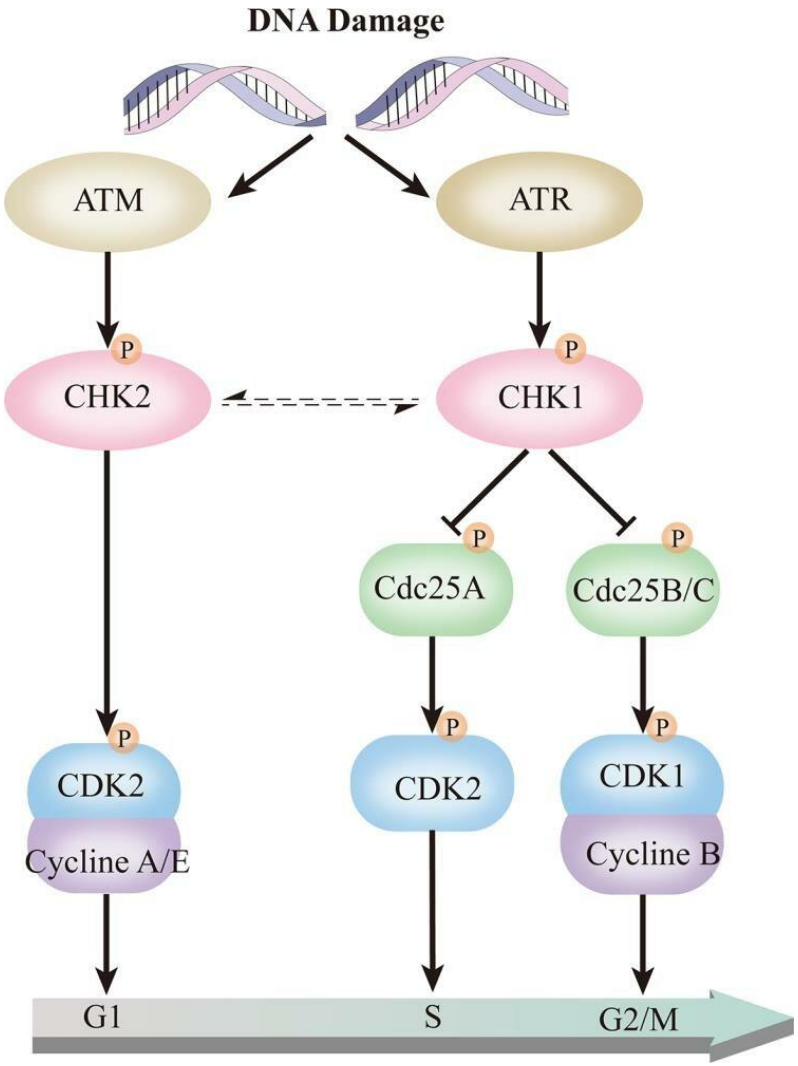
1. Occurs in G1, S and G2
2. ATM- ataxia teleangiectasia mutated
3. ATR – ataxia teleangiectasia and Rad3 related
4. BRCA1

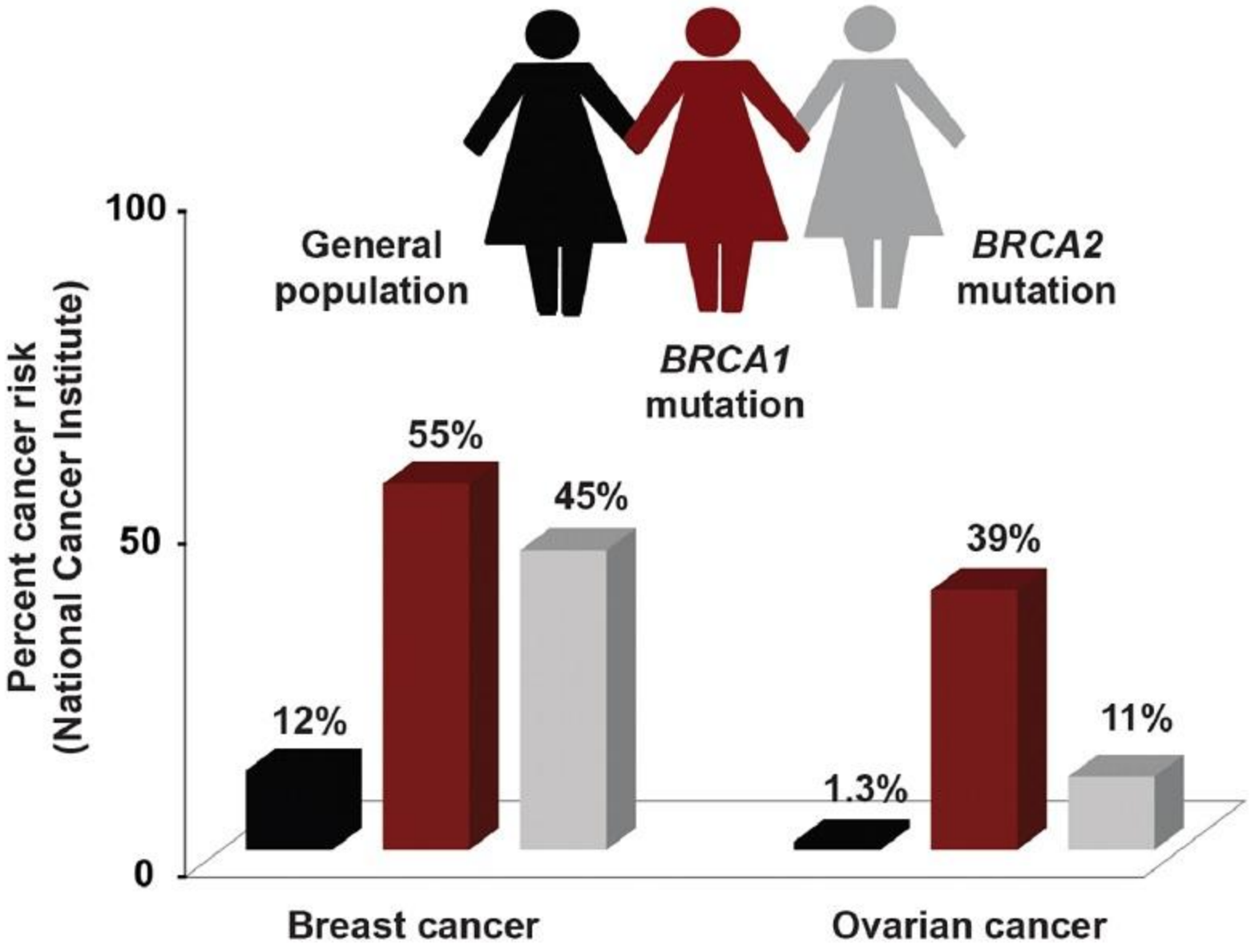


Biochemistry, Genetics and Molecular Biology » "DNA Replication-Current Advances", book edited by Herve Seligmann, ISBN 978-953-307-593-8

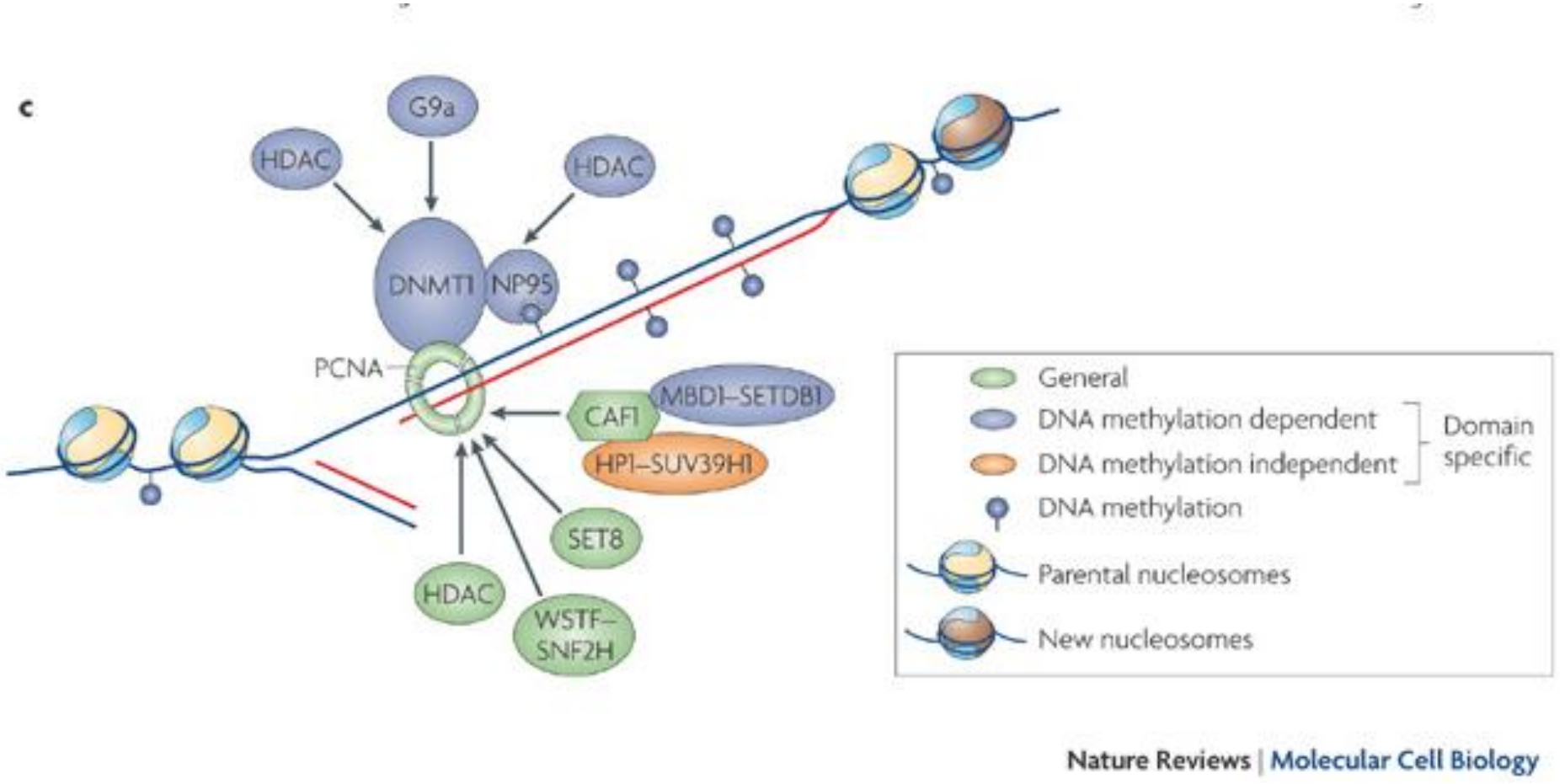


DNA repair
Cell cycle control
DNA replication
Transcriptional regulation
RNA metabolism
Senescence
Apoptosis




General population
BRCA1 mutation
BRCA2 mutation
Percent cancer risk (National Cancer Institute)
100
50
0
12%
55%
45%
1.3%
39%
11%
Breast cancer
Ovarian cancer

Epigenome restoration



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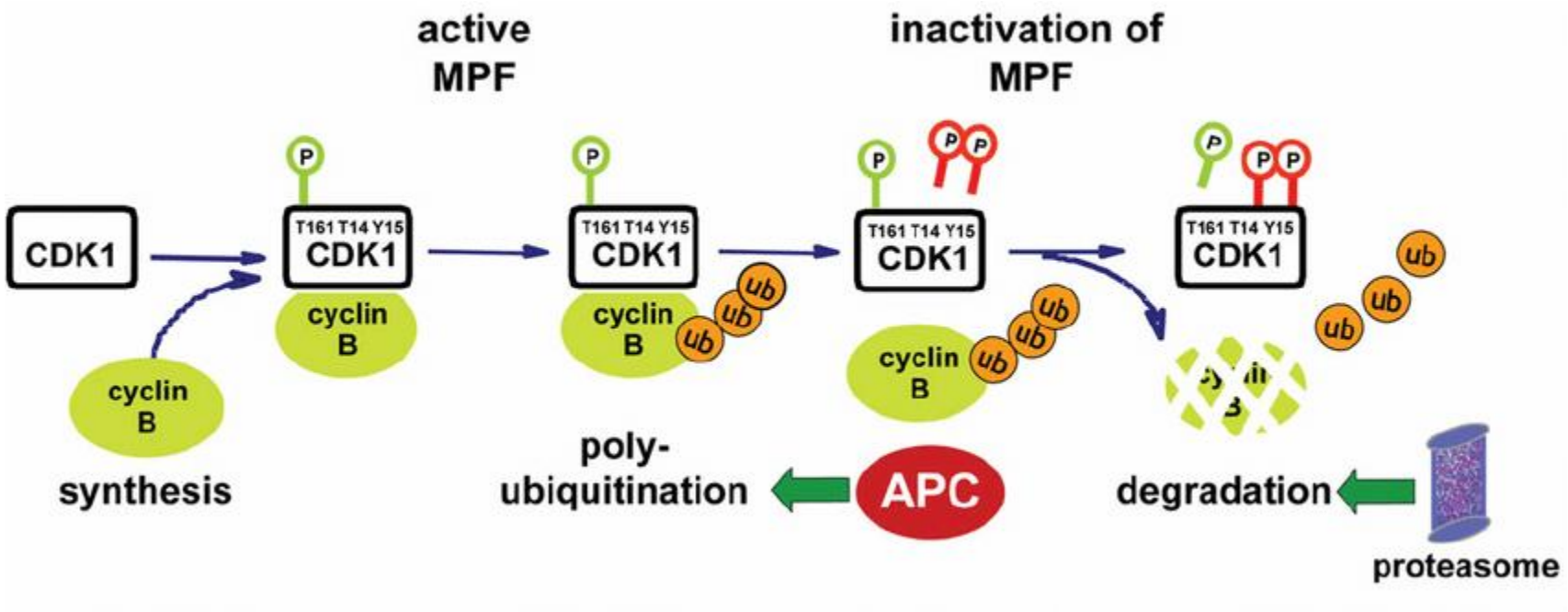
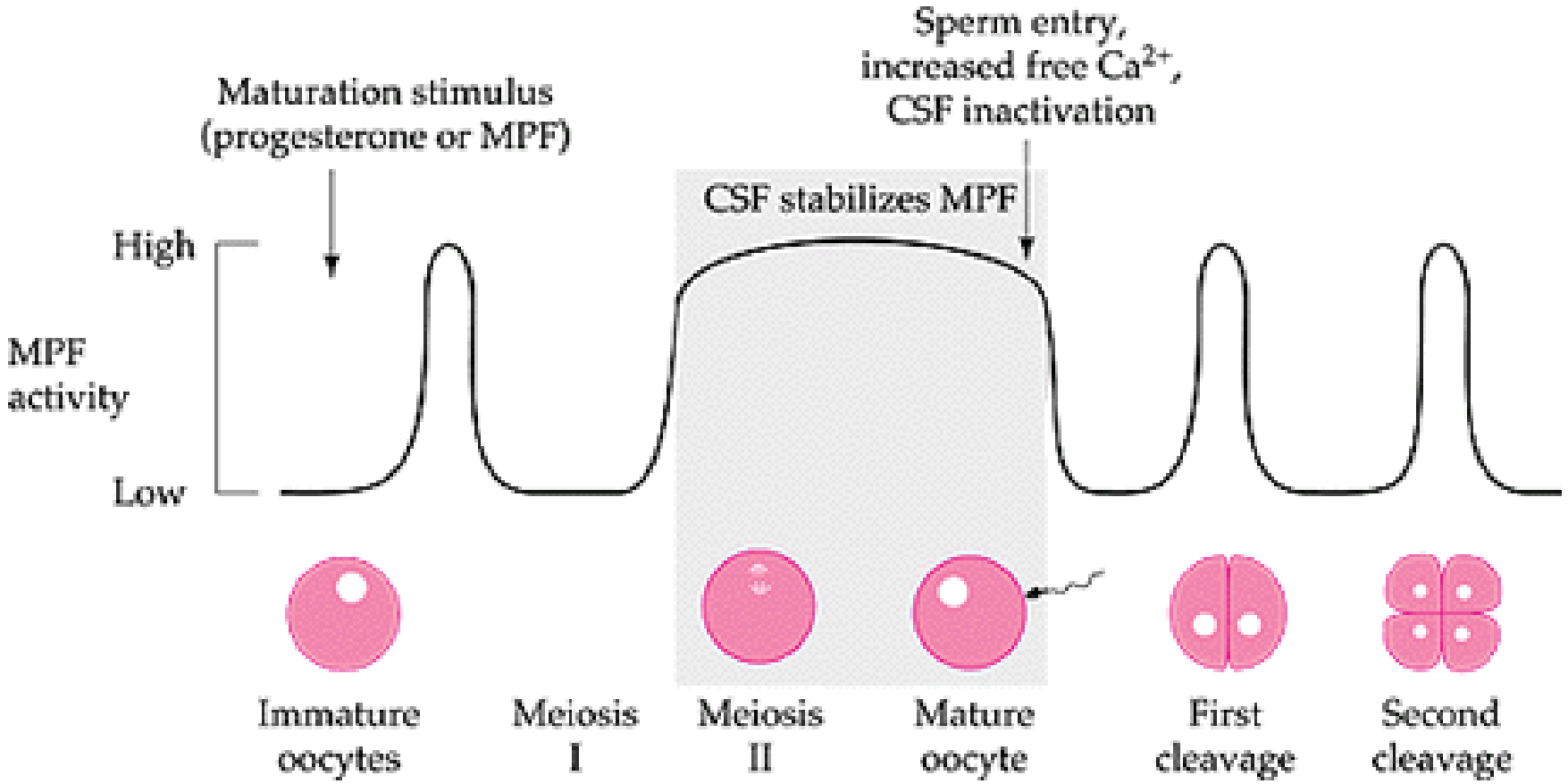
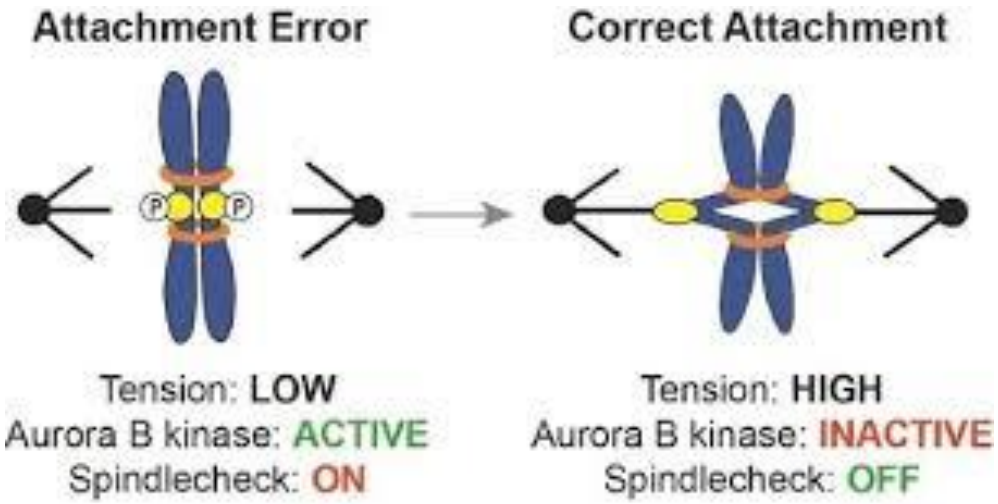
G2 to M phase switch – MPF – cyclin B/CDK1

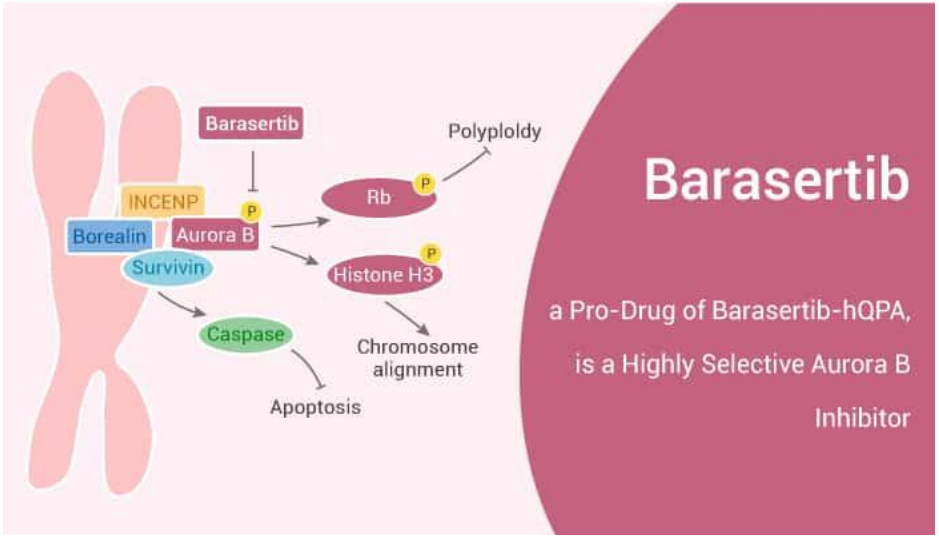


MPF in meiosis

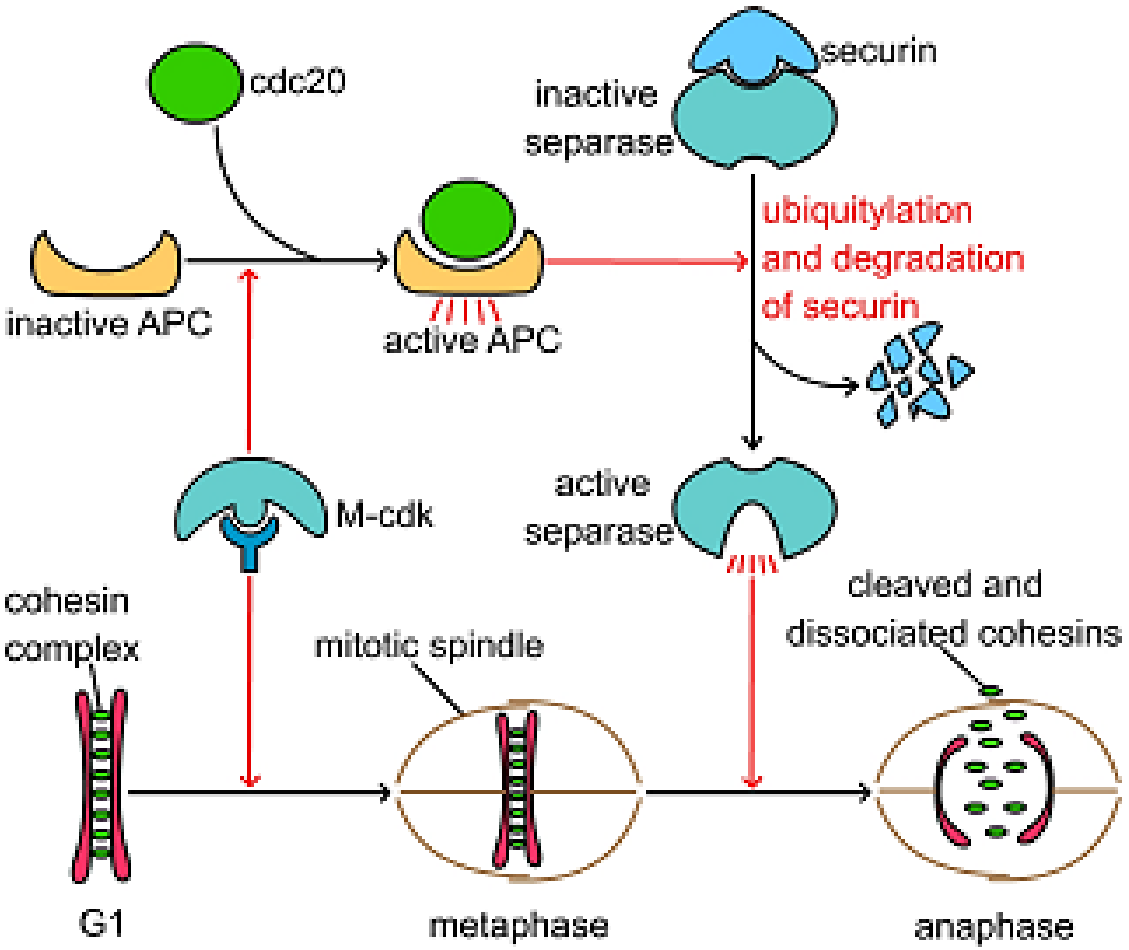


Mitotic spindle checkpoint





APC – anaphase promoting complex



Protooncogenes and supressors

- Protooncogenes – cycle progression
- CDK
- Cyclins
- Transcription factors
- Growth factors
- Receptors for growth factors and hormones
- Signaling molecules
- Antiapoptotic proteins

- Supressors – block the cycle
- Rb
- 53
- Cycle inhibitors
- Receptors for factors that block the cycle (TGFbeta)
- PTEN
- Proteins that repair DNA
- Proapoptotic proteins

Viruses and cell cycle

Viral disease	Viral	Cellular	Function
Simian sarcoma	v-*sis*	*PDGFB*	Platelet-derived growth factor B subunit
Chicken erythroleukemia	v-*erb-b*	*EGFR*	Epidermal growth factor receptor
McDonough feline sarcoma	v-*fms*	*CSF1R*	Macrophage colony-stimulating factor receptor
Harvey rat sarcoma	v-*ras*	*HRAS1*	Cell signaling, activation of MAPK cascade
Abelson mouse leukemia	v-*abl*	*ABL*	Protein tyrosine kinase
Avian sarcoma 17	v-*jun*	*JUN*	Transcription factor
Avian myelocytomatosis	v-*myc*	*MYC*	Transcription factor
Mouse osteosarcoma	v-*fos*	*FOS*	Transcription factor

After Strachan, T. and Read, A. (2003). *Human Molecular Genetics*. London: Garland Science.