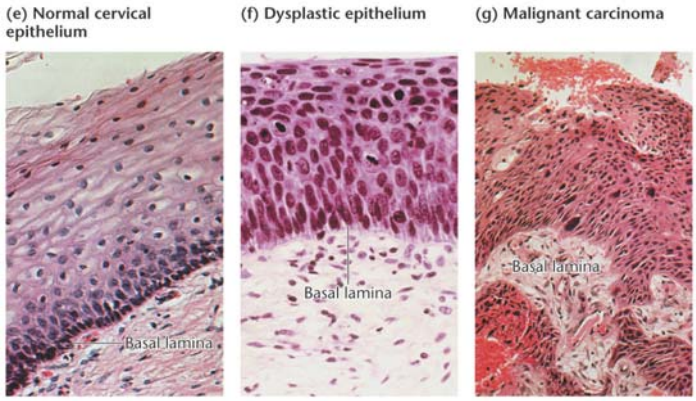
Genetics of Cancer

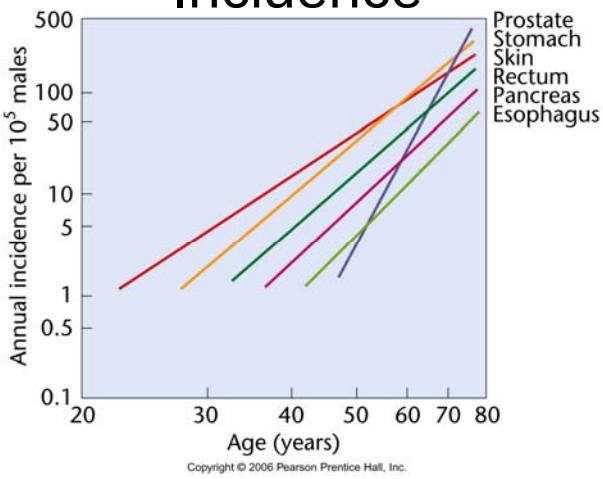
1. Properties of Cancer
2. Regulation of normal proliferation
3. Genes involved with cancer
4. Causes of Cancer
5. Cancer Therapies

Cancer



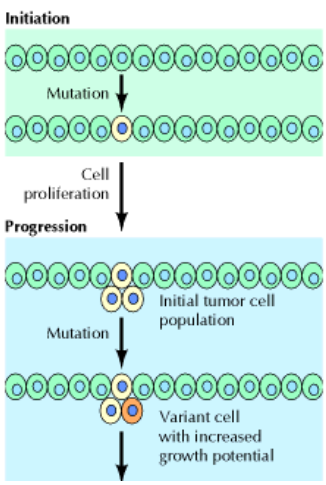
1. **Increased Proliferation**
   Increase cell division/decrease cell death
2. **Cell migration - metastasis**

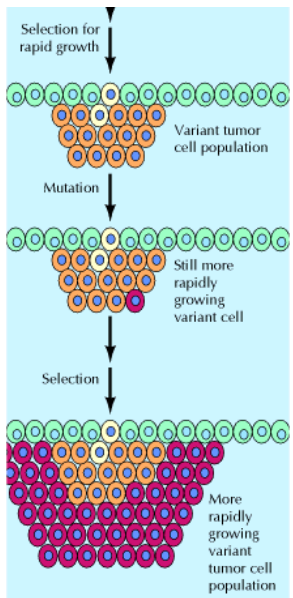
Incidence



Lifetime Risk
Men ~1 in 2 (~ 50%)
Women ~ 1 in 3 (~ 33%)

Clonal, progressive, genetic

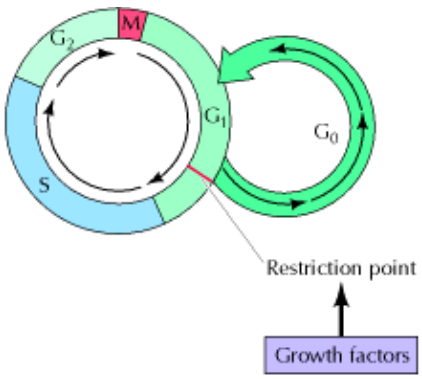




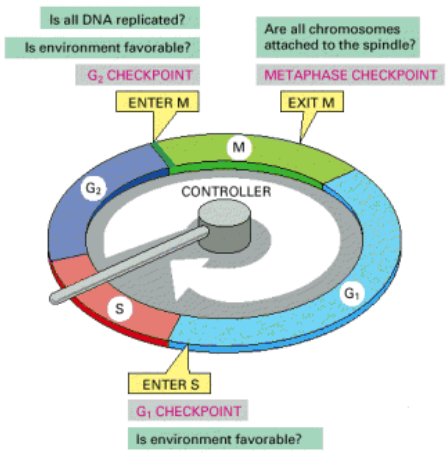
Regulation of normal cell proliferation

- Cell Cycle Checkpoints
  - "cell brake"
- Hormonal Regulation of Cell Growth
  - "accelerator"
- Apoptosis
  - "emergency brake"
- Genomic stability
  - "maintenance"

Cell Cycle Check points

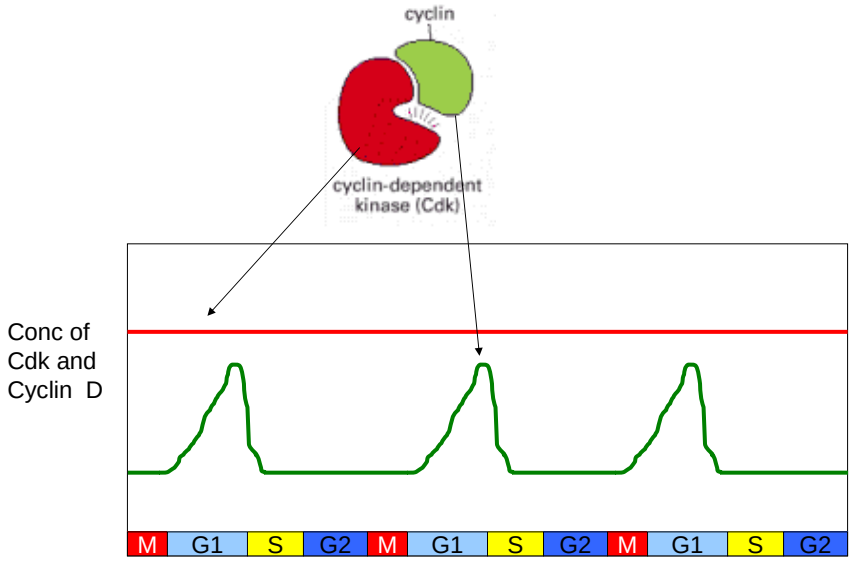


Cooper, The cell, a molecular approach, 2nd ed.

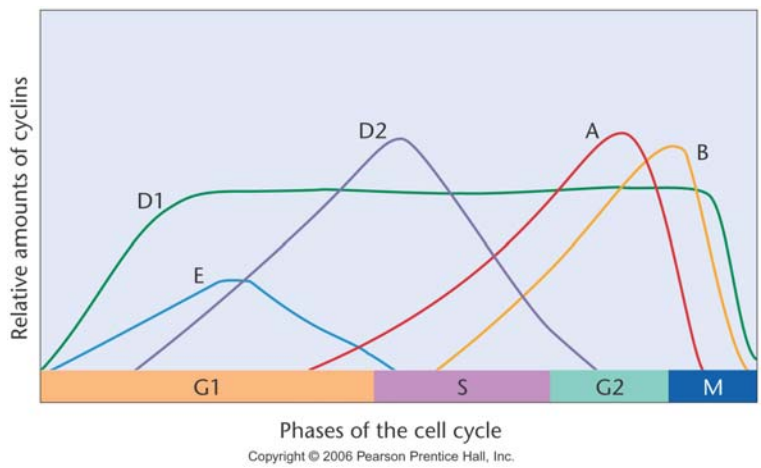


Alberts, Mol Biol of the Cell, 4th ed

Checkpoint Machinery

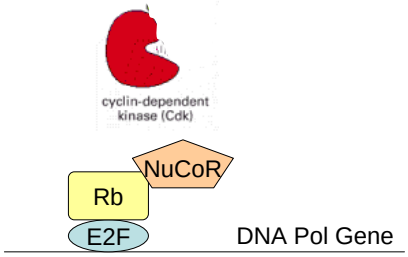


Different cyclins for different checkpoints



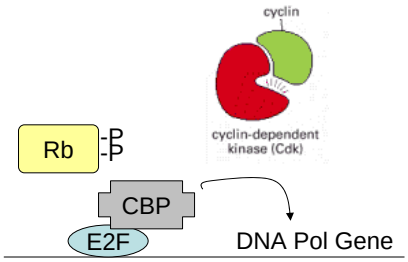
Cyclin/cdk targets
Rb example

G2 Cell



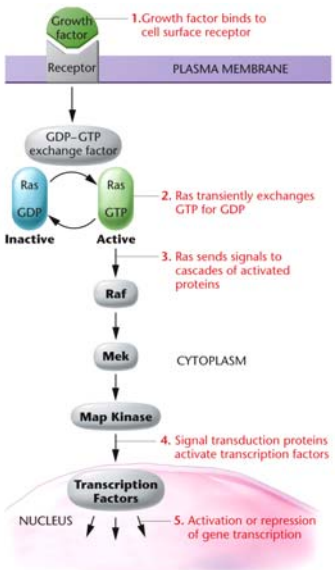
E2F activation domain masked
- No production of DNA polymerase

Late G1 Cell

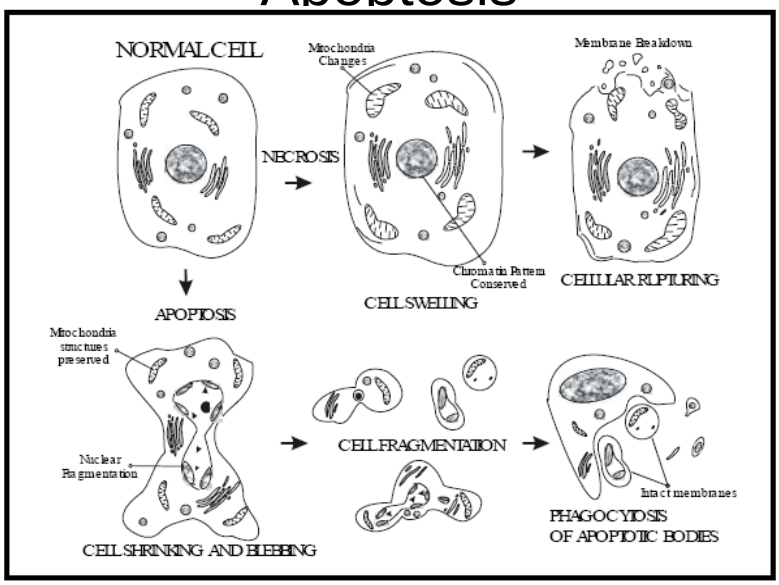


Rb phosphorylated by Cdk
Phosphorylated RB releases E2F
E2F recruits CBP
DNA polymerase gene transcribed

Hormonal Regulation

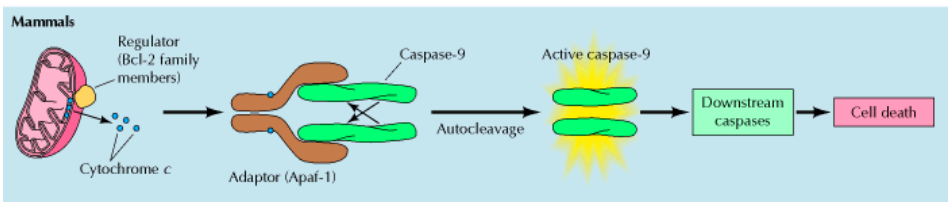


Apoptosis



http://plaza.ufl.edu/cleeuwen/LECTURE-6.PDF

Regulation of Apoptosis



Unregulated Cell division → DNA Damage → Activate p53 → Inhibits Bcl-2 → Release Cytochrome c

Excess Mutagens → DNA Damage

Defective DNA Repair → DNA Damage

Genomic Instability

- DNA Repair mechanisms
  - BER
  - NER
  - Others

Xeroderma – genetic defect in NER

Two types of Cancer Genes

Oncogenes

– dominant effectors of cancer

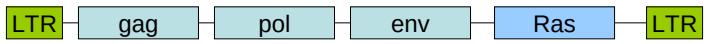
Tumor suppressor genes

– normally suppress cancer

– loss of both alleles triggers cancer. (null allele acts like a recessive effector of cancer)

Oncogenes

- Viral Oncogenes
  - Oncoviruses
    - Rous Sarcoma Virus - chickens
    - Harvey and Kirsten rat sarcoma viruses
    - Viral Oncogenes
    - Source – host genome

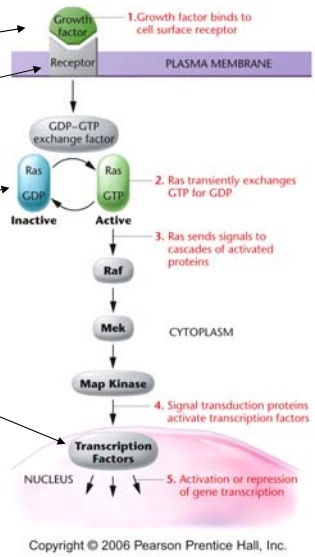


Mutation

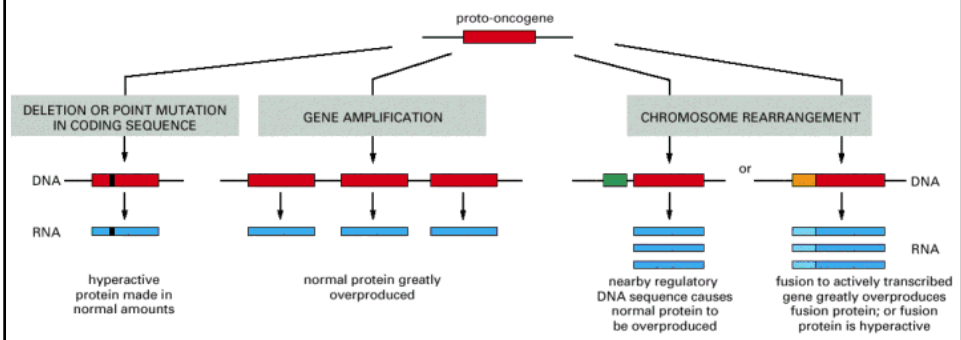
Proto-oncogenes → Cellular Oncogenes

Classes of cellular oncogenes

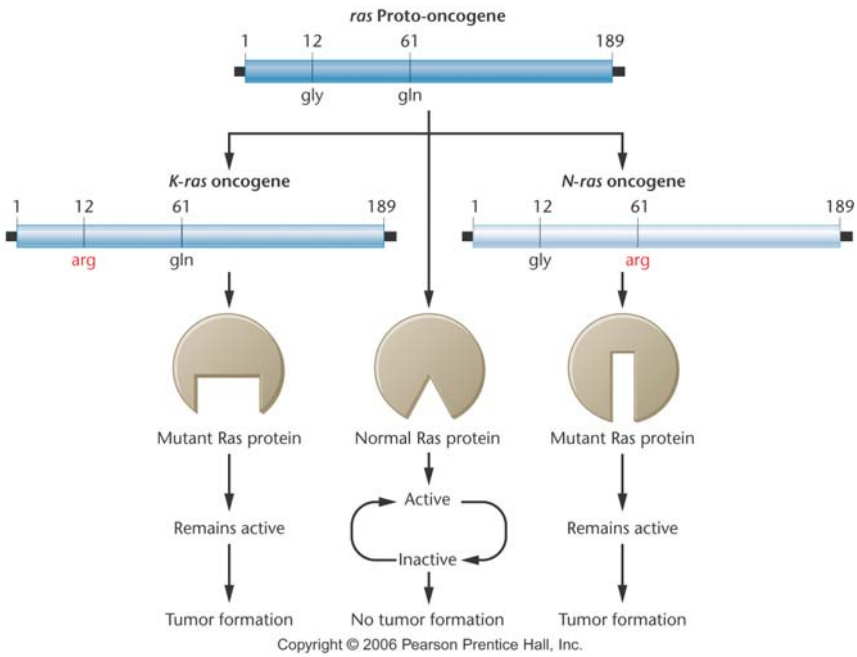
1. Growth Factors
2. Growth Factors receptors
3. Signal Transduction proteins
4. Transcription Factors



Mutations in proto-oncogenes



Alberts, Mol Biol of the Cell, 4th ed

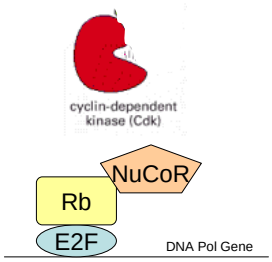


Classes of Tumor Suppressor Genes

- Genes involved in checkpoints
- Genes that stimulate apoptosis
- Genes important to genomic stability

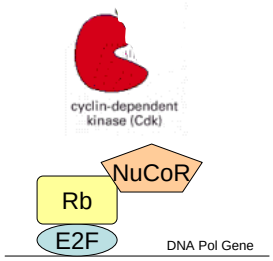
Genes involved in checkpoints Example Rb

2 copies Rb gene



Cell cycle inhibited

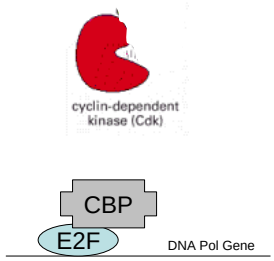
1 copies Rb gene



Cell cycle inhibited

Genetic Predisposition
Retinoblastoma

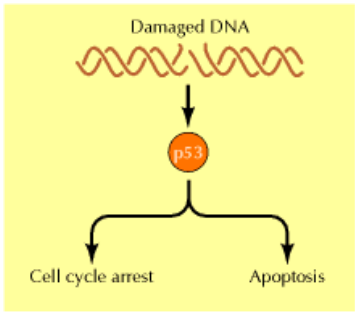
0 copies Rb gene



Cell cycle inhibited

Retinoblastoma

Genes that stimulate apoptosis example p53



DNA Damage → Activate p53 → Inhibits Bcl-2 → Release Cytochrome c

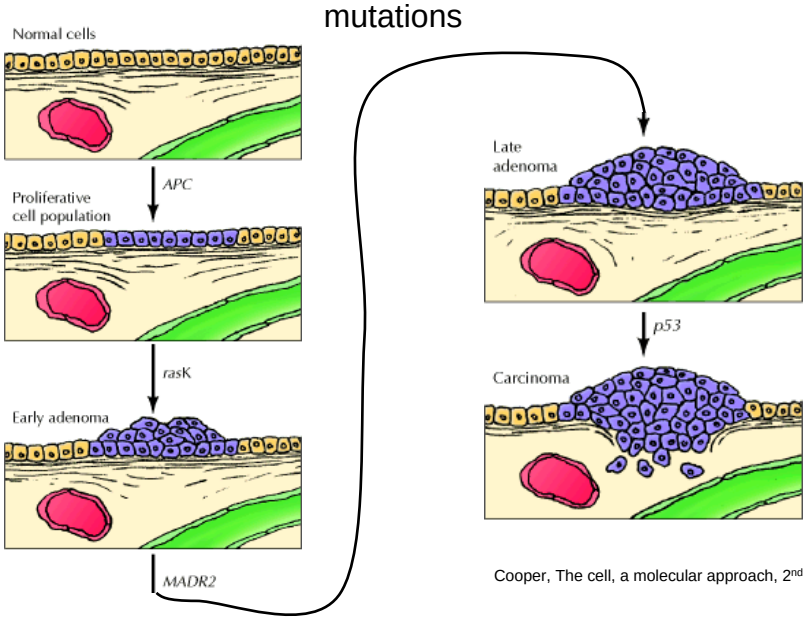
DNA Damage → Activate p53 → Induces p21 expression → P21 inhibits Cyclin/cdk → Rb not phosphorylated

Genes important to genomic stability

- Example
  - BRCA2 – repair of double strand breaks

AGE (years)	Cumulative Risk(%)
30 yrs	3.2%
40 yrs	19.1%
50 yrs	50.8%
60 yrs	54.2%
70 yrs	85%

Order progression of tumor suppressor and oncogene mutations



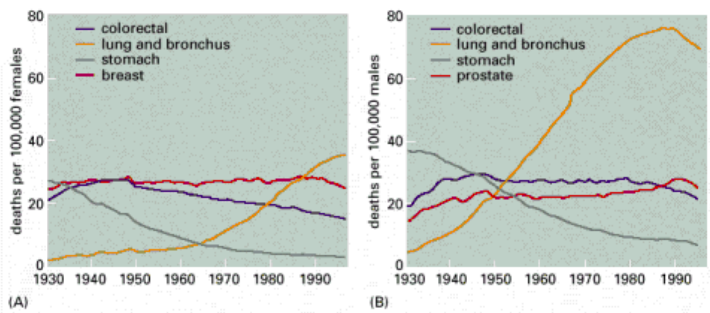
Cooper, The cell, a molecular approach, 2nd ed.

Epidemiology

Cancer Epidemiology

Cancer	**High Incidence**	**Low Incidence**
Breast Cancer	Hawaiians 1/1000	Palestinians .05/1000
Stomach	Japan .8/1000	Palestinians .03/1000
Lip	Canadian .15/1000	Japanese .001/1000

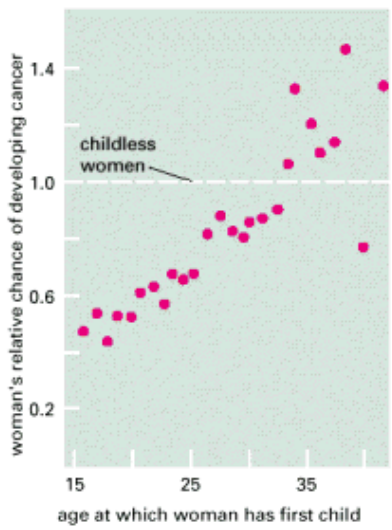
{New cases/year}



Causes of Cancer

- Carcinogens
  - Chemical mutagens
    - Tumor initiator
  - Non-mutagenic carcinogens (Tumor Promoter)
    - Phorbol esters (TPA)
- Tissue irritation
- Viruses
  - Papovavirus – uterine cancer
  - Epstein-Barr virus – Lymphoma
  - HIV – Kaposi sarcoma
- Genetic Predispositions

Other Causes



Treatments for Cancer

- DNA damaging treatments
  - Radiation
- Targeted Therapy
  - Tamoxifen (estrogen agonist)
  - Viruses that target p53 lacking cells
  - Target angiogenesis
  - Target oncogenes like BCR-ABL fusion
- Note cancers evolve in response to selective pressures of treatments.