Genetics of Cancer
Lecture 35
Alterations in different kinds of Genes cause Cancer

**Oncogenes**
dominant gain-of-function mutations promote cell transformation

**Tumor suppressor genes**
recessive, loss-of-function mutations promote cell transformation

**Mutator genes**
Usually recessive, loss-of-function mutations that increase spontaneous and environmentally induced mutation rates
What chromosomal events convert proto-oncogenes to dominantly acting oncogenes

- Point mutations (e.g., RAS)
- Partial deletion mutations (e.g., RTKs)
- Chromosomal translocations that produce novel fusion proteins (e.g., Bcr-Abl)
- Chromosomal translocation to juxtapose a strong promoter upstream and the proto-oncogene such that it is inappropriately expressed (e.g., cMyc, Bcl2)
- Gene amplification resulting in overexpression (e.g., N-Myc)
Point Mutation

LOH - Loss of heterozygosity

Non-Disjunction

Chromosome loss
Chromosome loss & duplication

Recombination

Deletion
Interchromosomal Recombination
Translocation
Gene Conversion
Sunlight
Pollution
Oxidation
Cigarette Smoke
Food
Excision Repair

Proteins Detect Damage

Enzymes Excise DNA Segment with Damage

DNA Polymerase Copies the Undamaged Strand

DNA Ligase Seals the ends together
Two thymine residues

Thymine-thymine dimer residue

Before

After

UV irradiation
Excision Repair

Proteins Detect Damage

Enzymes Excise DNA Segment with Damage

DNA Polymerase Copies the Undamaged Strand

DNA Ligase Seals the ends together
Xeroderma Pigmentosum: An Autosomal Recessive Disease

2000-fold increased risk of skin cancer
Complementation in fused cells reveals 7 genes that cause Xeroderma Pigmentosum.
Age at First Skin Cancer
There are Many Other Human Cancer Prone Syndromes Deficient in DNA Repair

If DNA Repair pathway is defective
Hereditary Nonpolyposis Colon Cancer
DNA Mismatch Repair Defect Syndrome inherited as Autosomal Dominant
Hereditary Breast Cancer Susceptibility DNA Recombination Repair Defect Syndrome inherited as Autosomal Dominant

BRCA2 Family Pedigree
Cells need time to repair DNA: DNA Damage induces Cell Cycle Checkpoints

- DNA damage signals cell cycle check points

- If the damage is too great to fix by repair a signal is sent for the cell to undergo suicide
DNA damage is sensed by sunlight, pollution, oxidation, and food. Cigarette smoke may also contribute. 

DNA damage triggers signal transduction, leading to the activation of kinases. This results in the p53 protein becoming phosphorylated (P) and activated. 

Further phosphorylation (P) of p53 leads to cell cycle arrest at G1, G2, and M phases, apoptosis, and increased DNA repair. 

The pathway shows a feedback loop, where activated p53 can inhibit its own expression, potentially regulating its activity.
Loss of p53 function occurs in more than 50% of human cancers!!

• These cancer cells are genetically unstable because they are unable to do the following:
  • Stop the cell cycling to allow time for DNA repair
  • Carry out efficient DNA repair
  • Undergo apoptosis
Li-Fraumeni Syndrome - Inheritance of one p53 null allele
DNA damage is sensed by factors such as sunlight, pollution, oxidation, food, and cigarette smoke. This signal transduction leads to the activation of kinases and the phosphorylation of p53, resulting in G1, G2, and M arrest of the cell cycle. Increased DNA repair and apoptosis are also activated. The phosphorylated p53 may further activate other genes involved in the cellular response to DNA damage.
Most fully blown cancers require inactivation of tumor suppressor genes and activation of oncogenes.

- **Inactivation of APC**
  - Tumor Suppressor genes

- **Activation of K-RAS**
  - Oncogene

- **Inactivation of p53**
  - Tumor Suppressor gene

**Take the case of Colon Cancer**

Normal epithelium → Early adenoma/dysplastic crypt → Late adenoma → Carcinoma → Metastasis

20 - 40 Years
Age at First Skin Cancer

The graph illustrates the cumulative cancer incidence (%) against age (years) for two populations: XP population and Non-XP population. The XP population shows a higher incidence of cancer at younger ages, while the Non-XP population has a delayed onset of cancer with a steeper curve starting around age 30 years.
Xeroderma Pigmentosum ~ 1/250,000

Interindividual Variation in DNA Repair Capacity

Wei et al., Clinical Chemistry, Vol. 41, No. 12, 1995
Good Luck for the Final Exam