Lecture 21
Cancer Genetics I

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"Cancer is, in essence, a genetic disease. Although cancer is complex, and environmental and other nongenetic factors clearly play a role in many stages of the neoplastic process, the tremendous progress made in understanding tumorigenesis in large part is owing to the discovery of the genes, that when mutated, lead to cancer."

Bert Vogelstein (1988)
NEJM 1988; 319:525-532.

Cancer Genetics: I

Lecture Goals

- Types of Genetic Alterations in Cancer
- Evidence that Mutations Cause Cancer
- Multistage Model of Carcinogenesis
- Oncogenes, Tumor Suppressor Genes, DNA Repair Genes

Cancer Arises From Gene Mutations

Germline mutations

Somatic mutations

Somatic mutation (eg, breast)

Types of Genetic Alterations in Cancer

- Subtle alterations
- Chromosome number changes
- Chromosomal translocation
- Amplifications
- Exogenous sequences

Subtle Alterations

- Small deletions
- Insertions
- Single base pair substitutions
  - (Point mutations)

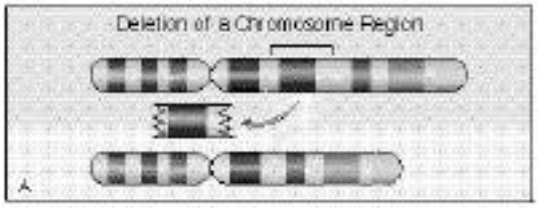
Point Mutations

Normal	THE BIG RED DOG RAN OUT.
Missense	THE BIG RAD DOG RAN OUT.
Nonsense	THE BIG RED.
Frameshift (deletion)	THE BRE DDO GRA.
Frameshift (insertion)	THE BIG RED ZDO GRA.

Point mutation: a change in a single base pair

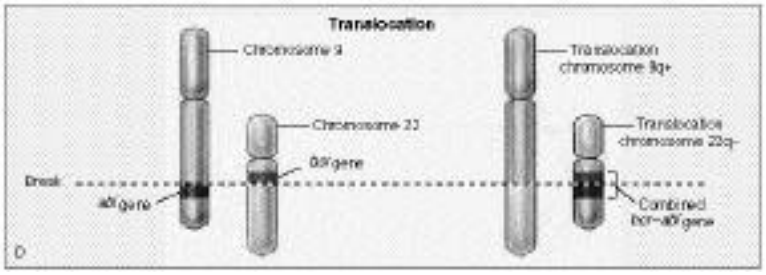
Chromosome Number Changes

- Aneuploidy
  - somatic losses or gains
- Whole chromosome losses often are associated with a duplication of the remaining chromosome.
- LOH
  - loss of heterozygosity



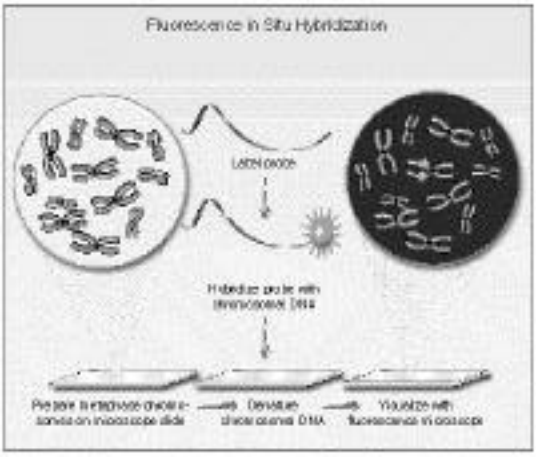
Chromosome Translocations

- Random translocations
  - breast, colon, prostate (common epithelial tumors)
- Non-random translocations
  - leukemia, lymphoma



FISH

- Certain chromosomal translocations are easily detected by FISH
- Fluorescent in Situ Hybridization
  - probes on different chromosomes fluoresce



Amplifications

- Seen only in cancer cells
  - 5 to 100-fold multiplication of a small region of a chromosome
- "Amplicons"
  - contain one or more genes that enhance proliferation
- Generally in advanced tumors

Exogenous Sequences

- Tumor viruses
  - contribute genes resulting in abnormal cell growth
- Cervical cancer
  - HPV (human papilloma viruses)
- Burkitt's lymphoma
  - EBV (Epstein-Barr virus)
- Hepatocellular carcinoma
  - hepatitis viruses

Review: Types of Genetic Alterations in Cancer

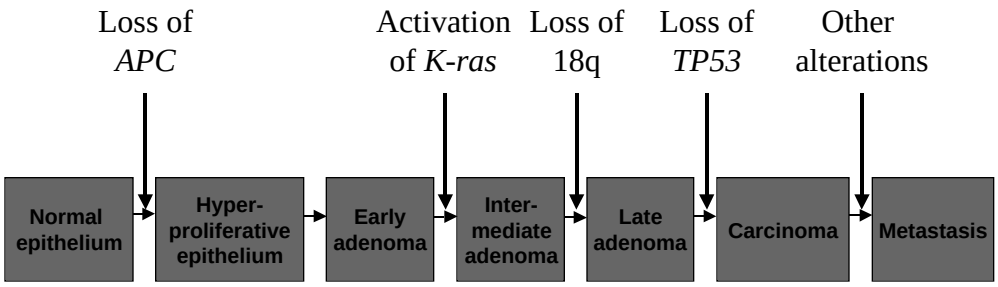
- Subtle alterations
- Chromosome number changes
- Chromosomal translocation
- Amplifications
- Exogenous sequences

Each type represents one of the mutations a cell can accumulate during its progression to malignancy

Evidence that Mutations Cause Cancer

- Most carcinogens are mutagens
  - *Not all mutagens are human carcinogens*
- Some cancers segregate in families
  - *Genes cloned, mutations lead to cancer in animals*
- Oncogenes and Tumor Suppressor Genes
  - *found in human tumors, enhance growth*
- Chromosomal instability
- Defects in DNA repair increase prob of cancer
- Malignant tumors are clonal

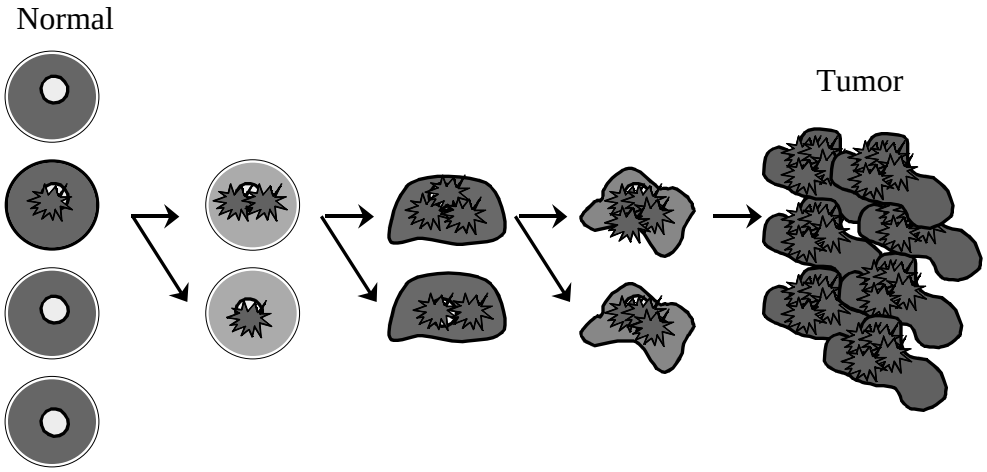
Multi-Step Carcinogenesis (eg, Colon Cancer)



Adapted from Fearon ER. ***Cell*** 61:759, 1990

ASCO

Tumors Are Clonal Expansions



"*No inkling has been found…of what happens in a cell when it becomes neoplastic, and how this state of affairs is passed on when it multiplies…. A favorite explanation has been that [carcinogens] cause alterations in the genes of cells of the body, somatic mutation as these are termed. But numerous facts, when taken together, decisively exclude this supposition.*"

Peyton Rous (1966)
in Les Prix Nobel

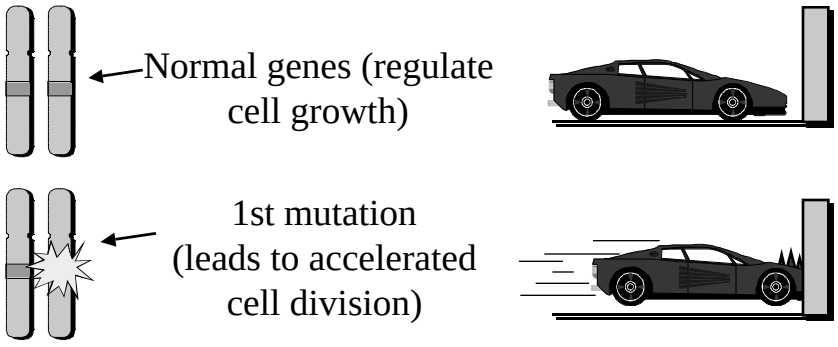
"The search for genetic damage in neoplastic cells now occupies a central place in cancer research…. Cancer may be a malady of genes, arising from genetic damage of diverse sorts -- recessive and dominant mutations, large rearrangements of DNA and point mutations, all leading to distortion of either the expression or biochemical function of genes."

J. Michael Bishop (1987)
Science 1997; 235:305-311

Oncogenes, Tumor Suppressor Genes, and DNA Repair Genes

- Oncogenes
- Tumor Suppressor Genes
- Retinoblastoma and the “2-hit Hypothesis”
- DNA Repair Genes

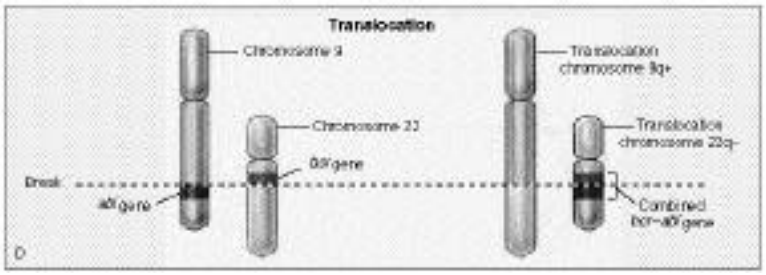
Oncogenes



1 mutation sufficient for role in cancer development

Oncogenes Activated in Non-viral Human Cancers

- Gene fusions / translocations
- Point mutations



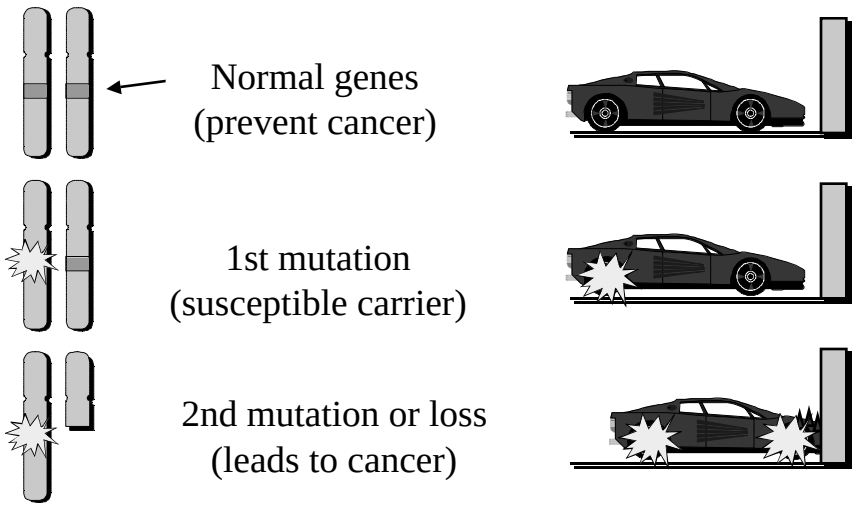
Effects of Oncogenes are Dominant

- Positive effect on growth
  - even in the presence of a normal (inactivated) version of the gene
- *Example*
  - Oncogenes derived from growth factor receptors confer the ability to bypass the growth factor requirement…independent growth.

Examples of Oncogenes

- RAS - activated in many cancers (colon)
- c-MYC - overexpressed in colon ca
  - amplified in lung, rearranged in lymphoma
- RET - MEN 2a
- MET - hereditary papillary renal cancer
- CDK4 - familial melanoma
- BCR/ABL - chronic myelogen leuk t(9;22)
- BCL2 - follicular lymphoma t(14;18)

Tumor Suppressor Genes



Tumor Suppressor Genes
Key Attributes

- Familial Cancer Syndromes
- Inactivation in Common Human Cancers
  - Loss of Heterozygosity
- "Recessive" at a cellular level
- Two-hit hypothesis

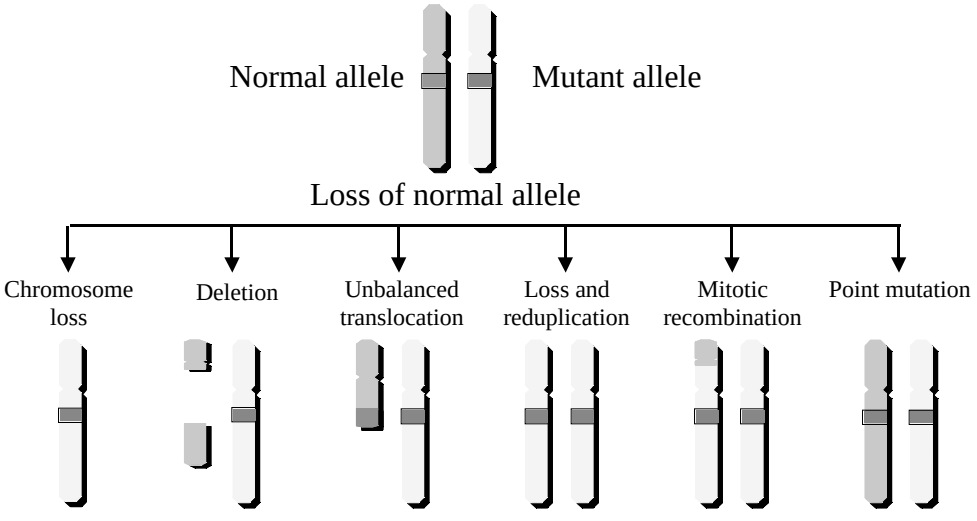
Tumor Suppressor Genes
Familial Cancer Syndromes

- Most familial cancer syndromes are related to Tumor Suppressor Genes
  - Retinoblastoma, FAP, Li-Fraumeni, Familial Breast-Ovarian, VHL, Melanoma, Tuberous Sclerosis...
- Only 3 known syndromes related to Oncogenes
  - RET, MET, CDK4
- Few DNA repair syndromes
  - XP, AT, Bloom, Fanconi, Werner, HNPCC

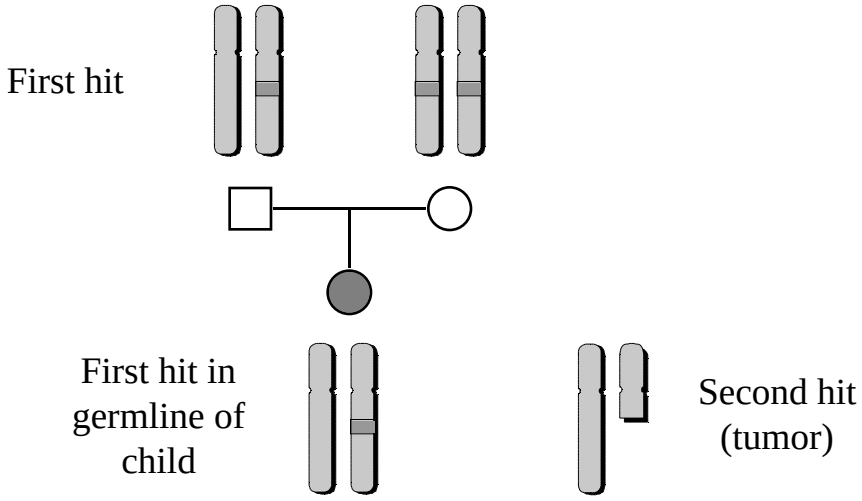
Tumor Suppressor Genes

- Loss of Heterozygosity (LOH)
- 2 copies of each gene
- 1 is lost or inactived
- Only 1 remains…
  - no longer heterozygous
  - one copy of a defective gene, same as no gene

Mechanisms Leading to Loss of Heterozygosity



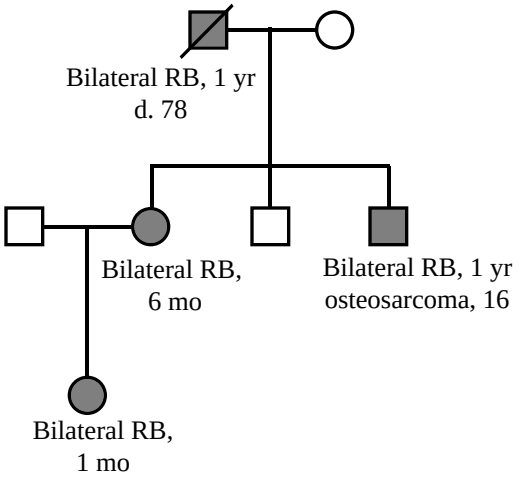
The Two-Hit Hypothesis



Features of Retinoblastoma

- 1 in 20,000 children
- Most common eye tumor in children
- Occurs in heritable and nonheritable forms
- Identifying at-risk infants substantially reduces morbidity and mortality

Genetic Features of Heritable Retinoblastoma

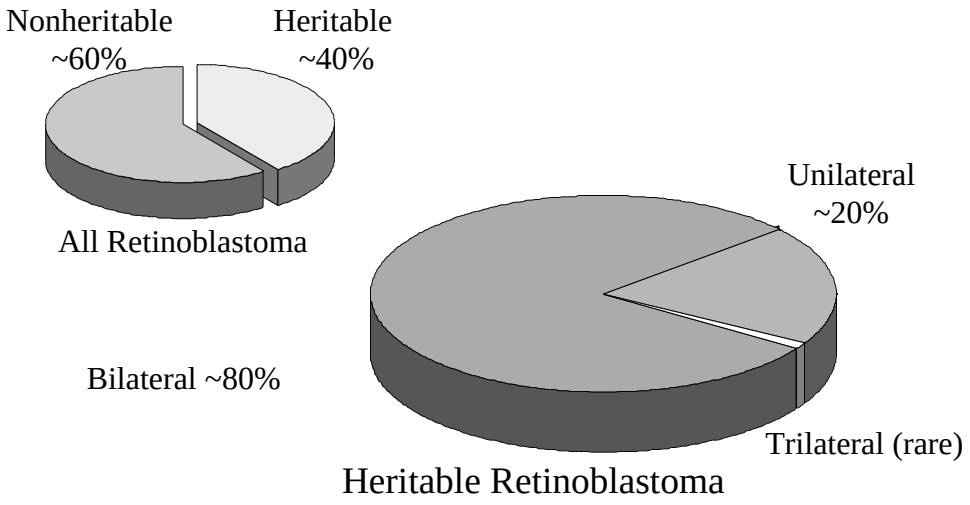


- Autosomal dominant transmission
- *RB1* gene on chr 13 (first tumor suppressor gene discovered)
- Penetrance >90%
- Prototype for Knudson's "two-hit" hypothesis

Nonheritable vs Heritable Retinoblastoma

Feature	Nonheritable	Heritable
Tumor	Unilateral	Usually bilateral
Family history	None	20% of cases
Average age at dx	~2 years	<1 year
Increased risk of second primaries	No	Osteosarcoma, other sarcomas, melanoma, others

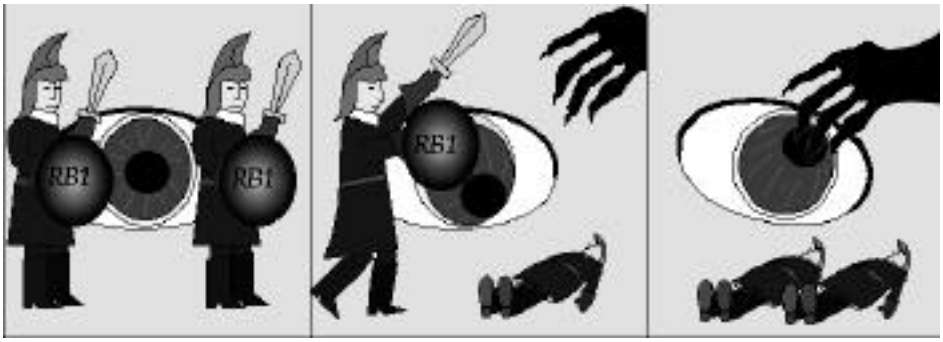
Presentations of Retinoblastoma



"The data presented here and in the literature are consistent with the hypothesis that at least one cancer, retinoblastoma, can be caused by two mutations…. One of these mutations may be inherited as a result of a previous germinal mutation…. Those patients that inherit one mutation develop tumors earlier than do those who develop the nonhereditary form of the disease; in a majority of cases those who inherit a mutation develop more than one tumor."

A. Knudson
PNAS 1971, p.823

Knudson's "Two-Hit" Model for Retinoblastoma



Normal	Predisposed	Affected
2 intact copies	1 intact copy 1 mutation	Loss of both copies

Modified from ***Time,*** Oct. 27, 1986

ASCO

The *RB1* Gene

- Large gene spanning 27 exons, with more than 100 known mutations
- Gene encodes Rb protein which is involved in cell cycle regulation

DNA Repair Genes

- DNA repair genes
  - targeted by loss of function mutations
- Differ from tumor suppressor genes:
  - TSG directly involved in growth inhibition or differentiation
  - DNA repair genes are indirectly involved in growth inhibition or differentiation

DNA Repair Genes

- Inactivation of DNA repair genes
  - increased rate of mutation in other cellular genes
  - proto-oncogenes
  - tumor suppressor genes
- Accumulation of mutations in the other cellular genes is rate limiting…
  - tumor progression is accelerated

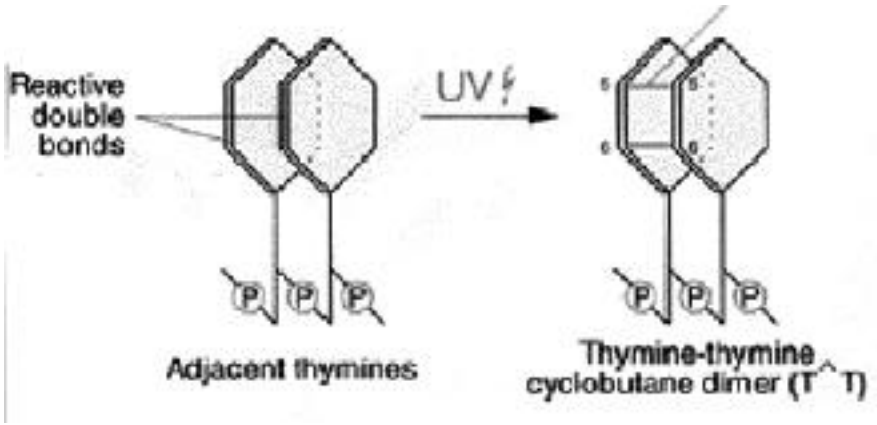
DNA Repair Genes

- Nucleotide Excision Repair
- Mismatch Repair
- Somatic Mutational Disorders

Nucleotide Excision Repair

- Xeroderma Pigmentosa
  - individuals are extremely vulnerable to UV light
- NER
  - removes wide array of unrelated DNA damage
- Repairs helix-distorting chemical adducts
  - adducts induced by carcinogens like
    - benz[a]pyrene
    - UV light

Nucleotide Excision Repair



Mismatch Repair

- Hereditary NonPolyposis Colorectal Cancer
  - increased incidence of cancers of the colon, endometrium, ovary, stomach, and upper urinary tract
  - autosomal dominant
- HNPCC due to germline mutations in mismatch repair genes
  - hMSH2, hMLH1, MSH6, (PMS1, PMS2)

DNA Mismatch Repair