

FAMILIAL CANCER

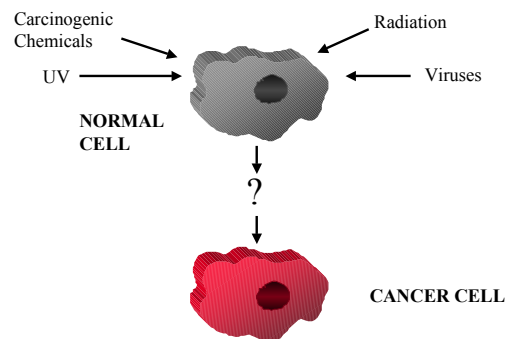
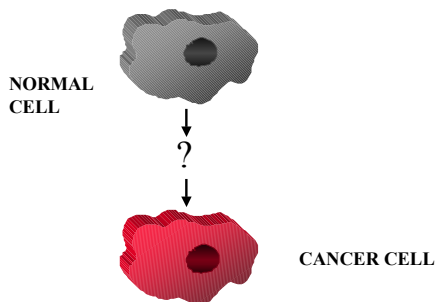
April 21, 2004

Jas C Lang PhD
lang.8@osu.edu

CANCER IS A GENETIC DISEASE

Is Cancer a Hereditary Disease?

What Causes Cancer?

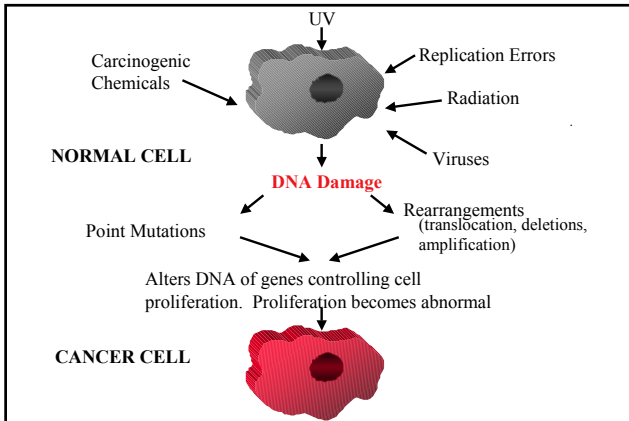


Cancer: Definition

- Cancer is the abnormal accumulation of cells caused by altering:
 - proliferation rate (deregulated)
 - death rate (altered apoptosis)
 - differentiation capacity (differentiation blocked)
 - DNA repair efficiency (DNA repair defective)

Altered Cell Proliferation and Cancer

- Each human cell contains approximately 30-40,000 genes
- Some genes are responsible for control of cell proliferation
- If these genes are altered, cell proliferation becomes abnormal
- Abnormal cell proliferation is a hallmark of cancer



How is Normal Cell Proliferation Controlled?

- Progression through the cell cycle and ultimately cell division is controlled by the regulated expression of genes
- Involves equilibrium between expression of genes responsible for positive regulation of cell proliferation and expression of genes responsible for negative regulation of cell proliferation

What Causes Abnormal Cell Proliferation?

(1) Abnormal expression of a gene which produces a positive stimulus for cell proliferation

- Increased expression
- Temporal deregulation
- Production of an abnormal gene product
- Combination of above

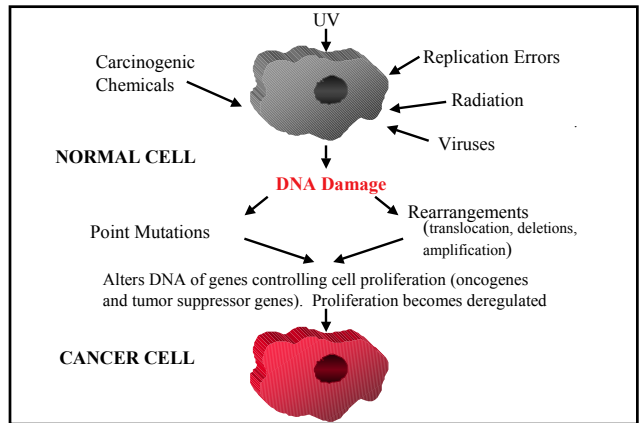
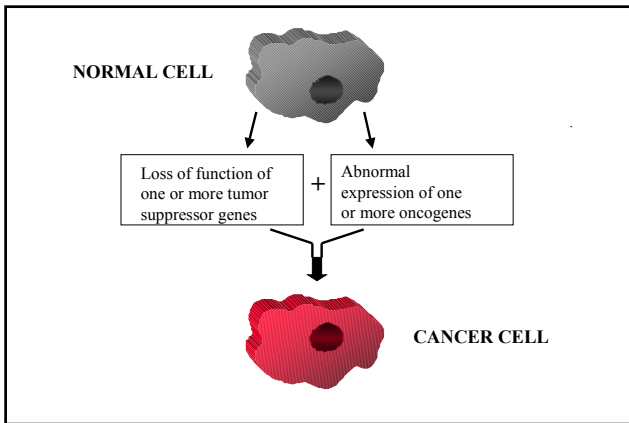
Genes which produce a positive stimulus for cell proliferation and whose abnormal expression is involved in the conversion of cells to a transformed phenotype are called **ONCOGENES**

What Causes Abnormal Cell Proliferation?

(2) Abnormal expression of a gene which produces a negative stimulus for cell proliferation

- Loss of gene product
- Mutation of gene product

Genes which produce a negative stimulus for cell proliferation and whose function must be inactivated for cell transformation to occur are called **TUMOR SUPPRESSOR GENES**



Is Cancer A Hereditary Disease?

-Overall, approximately 15% of cases of cancer have a hereditary component

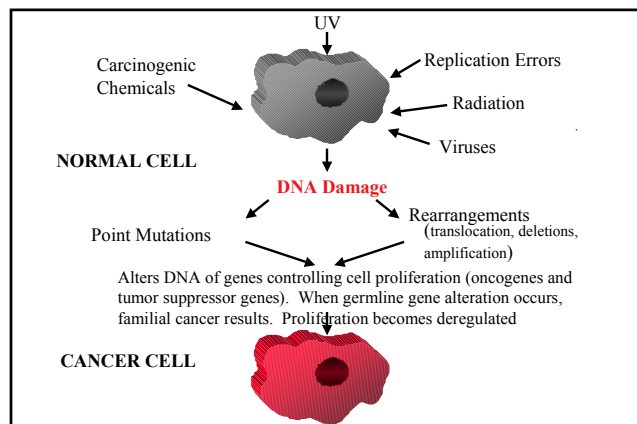
Familial (Hereditary) Cancer

Initiation of the disease is triggered by:

- The inheritance of a predisposing mutation in a tumor suppressor gene
- The inheritance of a predisposing mutation in an oncogene:
 - RET in cancer syndromes - Familial Medullary Thyroid Carcinoma (FMTC) and Multiple Endocrine Neoplasia Type 2A (MEN 2A)
 - MET in hereditary papillary renal cancer
 - CDK4 in familial melanoma
- The inheritance of a predisposing mutation in a DNA repair gene

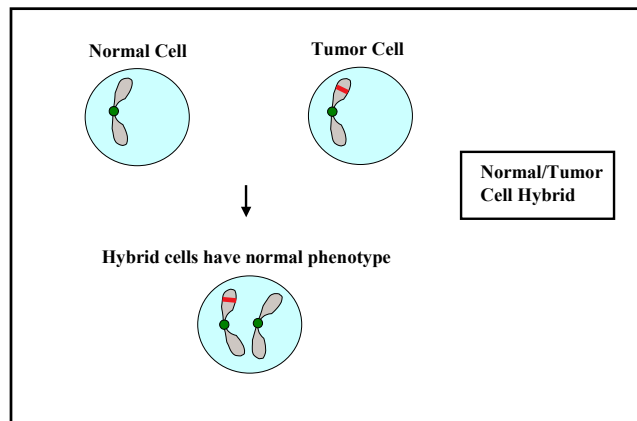
Familial Cancer (cntd)

- This single mutation is alone insufficient to cause cancer
- Further genetic alterations in other genes are necessary to produce cancer



Discovery of Tumor Suppressor Genes

- Somatic cell hybrids between tumorigenic and normal cells give no tumors in host animals



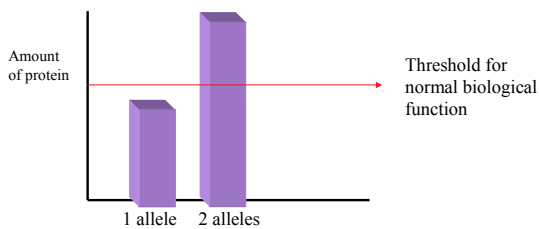
Discovery of Tumor Suppressor Genes (ctnd)

- Somatic cell hybrids between tumorigenic and normal cells give no tumors in host animals
- This evidence suggested that loss/inactivation of a gene is a necessary step in cancer development. Somatic cell hybrids were non-tumorigenic because the normal cell contributes a normal gene to the hybrid cell, restoring gene function.
- As additional evidence, consistent tumor associated deletion of specific chromosomal regions were also found

3 Mechanisms Cause Deficiency of Tumor Suppressor Gene Product

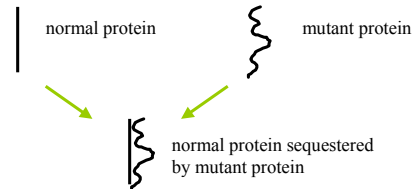
- Total inactivation by mutation or deletion of both alleles
- Partial inactivation by inactivation of one allele only. Product from remaining normal copy insufficient to support normal function ie: a gene dosage effect (haploinsufficiency)
- Dominant negative effect

Gene Dosage Effect



DOMINANT NEGATIVE EFFECT

For proteins which function as homodimers or greater (eg p53 protein as tetramer)



LEADS TO LOSS OF FUNCTION

Defective Suppressor Gene

Cancer Type

Retinoblastoma	Retinoblastoma
p53	Mutated in 50% human cancers
MLH1, MSH2	HNPCC
APC, DCC	Colorectal cancer
p16	Melanoma, leukemia, head and neck cancer

Defective Suppressor Gene

Inherited Cancer Syndrome

Retinoblastoma	Retinoblastoma
p53	Li-Fraumeni Syndrome
MLH1, MSH2	HNPCC
APC	Colorectal Cancer

Retinoblastoma

- In 1971, Alfred Knudson developed a theory to explain the genesis of retinoblastoma. Knudson noted that retinoblastoma occurred either as a single unilateral tumor in toddlers or as a multi-tumor bilateral disease in infants. Familial cases of retinoblastoma showed this bilateral pattern
- Based on this information he proposed a “two hit” hypothesis suggesting the development of retinoblastoma required two mutations in the same cell to occur. He predicted that one of these mutations was inherited in the germline, increasing the risk for development of the disease in these patients. This became known as the Knudson Hypothesis.

Retinoblastoma

- These mutations were later shown to represent the inactivation of both alleles of the retinoblastoma gene (Rb).
- Children inheriting a mutant allele develop normally until a second event causes inactivation of the second allele resulting finally in the development of retinoblastoma

Function of Retinoblastoma

- Retinoblastoma inhibits transcription of genes containing binding sites for E2F transcription factors

Inhibition of c-myc transcription by Rb



Li-Fraumeni Syndrome (p53)

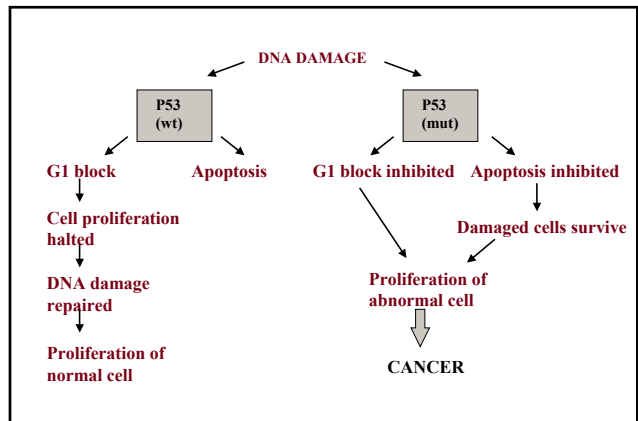
- Characterized by diverse neoplasms at many different sites in the body
- Inherit mutation in p53 tumor suppressor gene in one allele
- Mutation in single allele may inactivate p53 via dominant negative effect

P53

- Mutations in the p53 gene have been detected in more than 50% of sporadically occurring human tumors.
- p53 protein appears to be latent or inactive in normal cells and becomes activated for sequence-specific DNA binding by a variety of stimuli, including DNA damaging agents such as ultra-violet or gamma irradiation

P53 (ctnd)

- Induced expression of p53 after DNA damage results in two effects on the cell:
 - Cell growth arrest and repair of damage (inhibits proliferation)
 - Apoptosis (programmed cell death)



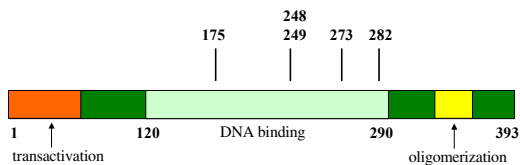
P53

- Function in cell cycle (proliferation):** p53 is a transcription factor. Inhibits function of genes that promote cell cycle progression
- p53 induces expression of the p21 gene. p21 binds to G1 cyclin - cyclin-dependent kinase (Cdk) complexes. Cdks phosphorylate specific substrates inducing cell cycle progression. Binding of p21 blocks this function
- Blocks progression of cells through the G1 phase of the cell cycle
- Function in apoptosis:** p53 induces expression of bax. Promotes apoptosis

Inactivation of P53 Function

- Mutation, deletion
- Interaction with viral proteins: adenovirus E1B, SV40 large T, HPV E6
- Interaction with cellular oncogene MDM-2. Some human sarcomas show amplified MDM-2. MDM-2 binds to p53 and causes p53 degradation. MDM-2 activity can be inhibited by binding of p14ARF. This function of p14ARF protects p53 and therefore stabilizes the protein

SITES OF MUTATION IN P53



Almost all mutations in p53 fall between codons 120-290

50% alter one of 5 codons shown

DNA Repair Genes

- Cancer may also develop due to defective DNA repair
- Results from mutations in DNA repair genes including breast cancer susceptibility genes (BRCA1, BRCA2) and hereditary non-polyposis colorectal cancer (HNPCC) susceptibility genes (MSH2, MLH1, PMS1, PMS2, MSH6)
- Mutant DNA repair genes unable to repair mutations occurring in oncogenes and tumor suppressor genes. Results in higher incidence in development of cancer.

Hereditary Non-Polyposis Colon Cancer (HNPCC)

- Autosomal dominant inherited genetic disease accounting for approximately 15% of colorectal cancers
- HNPCC patients also at increased risk for development of cancer of the endometrium, small intestine, ovary, stomach, and brain
- Mean age to development of colorectal cancer is early to mid 40's but may occur as early as 20's or teenage years

Hereditary Non-Polyposis Colon Cancer (HNPCC)

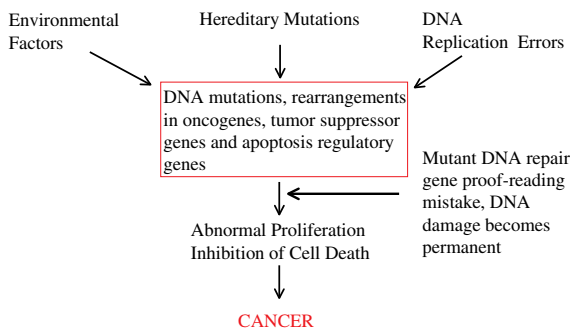
- HNPCC may be the most common form of familial predisposition to cancer
- Lifetime risk for development of any cancer is 91% (men) and 69% (women). For colorectal cancer, 74% (men), 30% (women).

Hereditary Non-Polyposis Colon Cancer (HNPCC)

- Result of mutation in a DNA repair gene controlling mismatch DNA repair. Genes are DNA proof-readers which control repair of DNA damage.
- 2 DNA repair genes found mutated in 64% of HNPCC
Mutation in hMSH2 in 31% HNPCC
Mutation in hMLH1 in 34% HNPCC
- Mutations in hPMS1 (rare, one family) hPMS2 (4%) and hMSH6 (rare, a few families) also found

Hereditary Non-Polyposis Colon Cancer (HNPCC)

- Inefficient DNA repair results in permanent mutations in growth regulatory genes (oncogenes and tumor suppressor genes)
- Knockout mice lacking MSH2 gene develop colonic cancers with 70% incidence of APC inactivation
- HNPCC cells may contain 100,000 mutations.



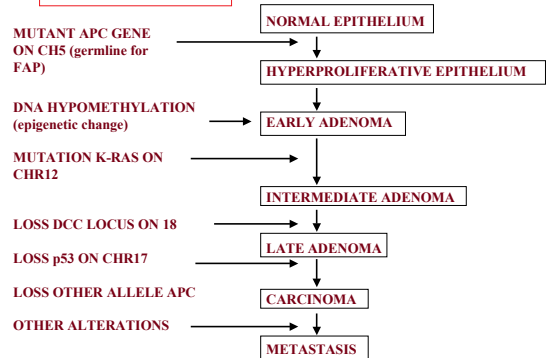
The Multi-Step Nature of Cancer

- Development of cancer is a multi-step process, involving an estimated 6-12 changes in key regulatory genes.
- Development of cancer involves alterations to multiple signal transduction pathways in the cell. Example: **Colorectal cancer**.
- Development of cancer involves alterations to multiple genes within a signal transduction pathway. In many cases these alterations may be redundant. Therefore no selective pressure exists to alter all genes in the same pathway. Example: **Head and neck cancer**.

Multi-Step Development of Colorectal Cancer (example of multiple pathways targeted)

- The hereditary cancer syndrome Familial Adenomatous Polyposis Coli (FAP) occurs in individuals who inherit a mutation in the APC gene
- FAP may be used as an example to illustrate the multi-step nature of cancer development
- In FAP a number of different gene pathways are altered, usually over a period of 20-30 years, finally resulting in the development of colorectal cancer

Colorectal Cancer



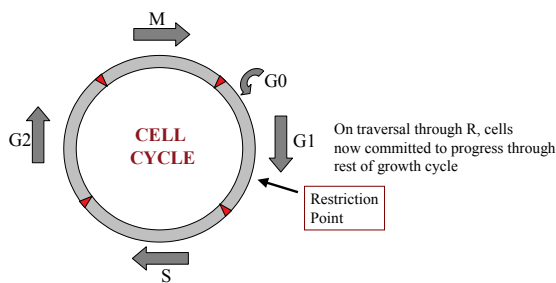
Multi-Step Development of Squamous Cell Carcinoma of the Head and Neck (example of multiple genes targeted in same pathway)

- Originates on surface of the epithelial lining of the upper aerodigestive tract
- Male to female ratio approximately 2:1 to 4:1, depending on the site
- Strong association with alcohol and tobacco (smoking or chewing abuse)

Multi-Step Development of Squamous Cell Carcinoma of the Head and Neck (example of multiple genes targeted in same pathway)

- Synergistic effect of tobacco + alcohol
- High mortality: 5-year survival rate 35-50%
- High morbidity: disfiguring, impaired speech, breathing, ability to eat

RETINOBLASTOMA AND THE CELL CYCLE



RB is a target (directly or indirectly) in the process of tumorigenesis

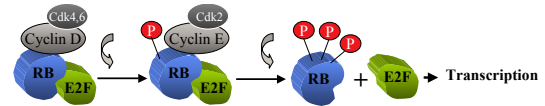
**Alteration to the Retinoblastoma Pathway in Cancer

- Oncogene cyclin D1 is a member of the cyclin gene family.
- Cyclin D1 associates with kinase CDK4 (cyclin dependent kinase 4). Association causes activation of the kinase which is then capable of phosphorylating target substrates and allowing progression through the cell cycle.
- Major substrate for cyclin D1/CDK4 is the retinoblastoma gene. Cyclin D1/CDK4 and retinoblastoma form a protein complex. Cyclin D1/CDK4 and cyclin E/CDK2 then sequentially phosphorylate Rb and causes Rb inactivation

****Alteration to the Retinoblastoma Pathway in Cancer**

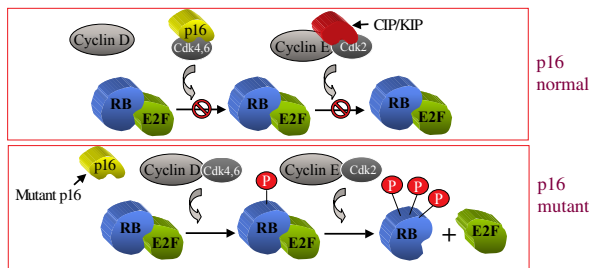
- Overexpression of cyclin D1 causes an equilibrium shift towards hyperphosphorylation of Rb and therefore inactivation of Rb resulting in deregulated progression through G1
- Tumor suppressor gene p16 can protect retinoblastoma from inactivation by binding to CDK4. When p16 is inactivated by mutation, deletion or hypermethylation, retinoblastoma is no longer protected from inactivation.

Inactivation of Retinoblastoma by Overexpression of Cyclin D1



Overexpression of cyclin D1 causes inactivation of retinoblastoma by phosphorylation and induces cell proliferation

Inactivation of Retinoblastoma by Mutation of p16



Mutant p16 is unable to protect retinoblastoma from inactivation by phosphorylation

Multi-Step Development of Squamous Cell Carcinoma of the Head and Neck (example of multiple genes targeted in same pathway) (ctnd)

- Head and neck cancer is caused in part by gene alterations in the retinoblastoma pathway that result in inactivation of retinoblastoma
- This pathway may be altered at multiple points. Examples are:
 - Overexpression of oncogene cyclin D1
 - Inactivation of tumor suppressor gene p16

Familial Cancer (Summary)

- Hereditary predisposition accounts for approximately 15% of all cancers. Inherit mutation in:
 - Tumor suppressor gene
 - Oncogene
 - DNA repair gene
- Mutation results in predisposition to cancer. Does not cause cancer.
- Cancer development is a multi-step process. Additional mutational events are necessary before cancer develops

Familial Cancer (Summary) (ctnd)

- 6-12 mutational changes may be necessary. Gene changes may occur in oncogenes, tumor suppressor genes, apoptosis regulatory genes, DNA repair genes or genes controlling cell differentiation.
- Cancer is a complex disease because:
 - 1) More than 1 pathway is altered to cause the disease
 - 2) Different genes in each pathway may be altered even in the same type of cancer
- Cancer is also a multi-factorial disease - both genetic and environmental factors contribute to development of the disease