

Tumor Genetics

- Cancer cells contain multiple alterations in the number and structure of genes and chromosomes
- Majority of genetic alterations are acquired by mutations in somatic cells
- Mutations may be point mutations (insertions, deletions) that may lead to increased or decreased gene expression or to novel gene products (dysregulation), translocations and inversions

- Infection by viruses alter genome (add new sequences, mutate existing sequences and cause insertions, deletions and rearrangements (*c-myc* translocations with EBV infection)
 - Oncogene insertion
 - Tumor suppressor gene inactivation
- <u>Epigenetic changes</u> = stable alterations in gene expression without changes in DNA sequence (plasmid-like alterations)

Cancer as a Genetic Disease

- DNA sequencing demonstrates that there are many point mutations in tumor cells (> 100's)
 - Only a small # of cancers are caused by mutations inherited in the germline- most from somatic mutations.
 - · Somatic mutations may enhance effects of inherited potential

Genetic Alterations in Cancer

- There generally have to be greater than 1 mutation for cancer to occur- can happen in a single gene or within a few genes
 - Point mutations- due to base exchanges in DNA (tansitions=pyr→pyr, pur→pur, or transversions= pyr→pur)
 - Lead to codon changes
 - » SILENT mutations- different codon same AA- may affect stability of mRNA but not protein
 - » MISSENSE mutations- change in AA- increased or decreased activity or unchanged activity depends on where alteration occurs in peptide

• Insert table 2.1

Viral genomes

- DNA viruses
 - Replicate in nucleus
 - Replicate as episomes, but in cancer cells probably integrate into host genome
 - These insertions usually disrupt normal genes
 - » Also viral genome is usually truncated so no productive virus is produced

• Retroviruses

- RT \rightarrow RNA into DNA and moves to nucleus and integrates
 - Affects gene expression near insertion site and may cause over expression

Other gene effects

- · Chromosomal Translocations-- c-myc in EBV
- Chromosomal Inversions -Usually happens within one chromosome may place a "silent gene" near the promotor region of another gene and up regulate that gene expression
- · Polyploidy and Aneuploidy -
- · Gene amplification-

Inherited pre-disposition to Cancer

· Pre-disposition to cancer is inherited

Autosomal dominant

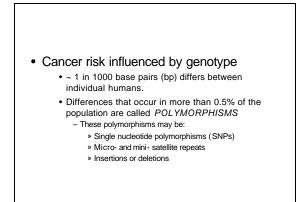
- » High penetrance (retinoblastoma, breast)
- » Lower age at onset
- » May occur at multiple sites
- » May be associated with birth/developmental defects
- » Caused by inherited mutation in a single gene
- » Affected genes usually tumor suppressor genes
- » By themselves do not cause cancer but it the first step of several mutations that are required

Recessive inheritance

- Initially affected by symptoms other than cancer and cancer appears later
- Cancer appears at relatively early age (like dominant cancers)
 - » xeroderma pigmentosum, ataxia telengiectasia, fanconi anemia, Bloom and Warner syndromes
- Predisposition to cancer caused by mutations inactivating BOTH copies of same gene
 - Genes involved usually important in cell protection and DNA repair

• Insert table 2.2 & 2.3

- Inheritance of mutated genes (either dominant or recessive) increases risk of developing cancer during one's lifetime to ~ 100% compared to spontaneous somatic mutations that would be very low
- Inherited cancers account for only about 10% of all cancers



• Insert table 2.4

- 50% of some European populations lack the gene for GSTM1 (glutathione transferase enzyme that metabolize xenobiotics)
- = "null allele" because no enzyme activity is present
 GSTM1 helps to metabolize benzopyrene, one of carcinogens in cigarette smoke
- GSTM1 -/- individuals who smoke are at higher risk of getting lung cancer

Cancer Genes

• In the late stage of progression a cancer cell may have several hundred genes mutated or rearranged

- Tumor suppressor genes-
 - » Function decreased in cancer either by mutations or epigenetic silencing
- Oncogenes-
- » Activated by mutations (growth factor genes) - DNA repair and checkpoint genes-
 - » Defects in these "caretaker" and "gatekeeper" genes increase rate of mutations
- Risk modulating genes-
- » Indirectly involved in cancer- influence level of active carcinogens, activity of immune response, level of hormones and growth factors - Execution genes-

 - Imp't after cancer established; induced as a consequence of activation of oncogenes (rarely by mutations)
 - » Not necessary for survival but for growth, invasion, metastasis

- Is there a "cancer gene"?
 - Some cases (retinoblastoma= RB1 {tumor suppressor} and Burkitt's lymphoma= myc *{oncogene})* in which there is direct evidence of a specific gene, but most other instances there is a combination of gene effects with environmental effects that interact to lead to cancer

Accumulation of Genetic and Epigenetic changes in Cancer

- Advanced cancers containmany genetic changes
 - At which stage of progression were they acquired??
 - Hard to tell
 - Slow progression
 - » Accumulation with age
 - » Need 4-5 "hits" necessary for cancer development
 - Most genetic changes due to somatic mutations, but

 - predisposition to cancer is also inherited May also be due to germ-line mutations in repair genes or
 - "caretaker" genes
 - Genomic instability in advanced cancers (is this required for progression/development??)

Tumor Viruses

• DNA and Retroviruses

- Integration usually necessary

- Carry oncogenes & insert into actively transcribed area (oncogenes vs proto-oncogenes)
- Carry promotor regions that activate quiescent genes
- Integration causes "mutation" in normal gene
- Infection causes translocation of oncogenes

DNA Damage and DNA Repair

• DNA continuously damaged

- Chemical modifications - Loss of bases
- Single strand/double strand breaks - Intra- and Inter-strand cross-links
- DNA replication important for incorporation of incorrect bases
 - Oxidative stress important in mutations
 - Spontaneous deamination of cytosine, etc...

Repair Mechanisms

· Glycosylases -

- remove damaged bases
- · Apurinic/apyrimidinic endonucleases -prepare sites lacking bases for short patch or long patch base excision repair
- · Nucleotide excision repair systems-- Carcinogen adducts and pyrimidine dimers (UV light)
- · Metallothioneins & Glutathione transferases -- Protect against reactive O2 species
- · Apoptosis-- Cell cycle check points (stress, viral infections)