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
- Epigenetic changes = 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→ 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

- Cancer risk influenced by genotype
  - ~ 1 in 1000 base pairs (bp) differs between individual humans.
  - Differences that occur in more than 0.5% of the population are called *POLYMORPHISMS*
    - These polymorphisms may be:
      - » Single nucleotide polymorphisms (SNPs)
      - » Micro- and mini- satellite repeats
      - » Insertions or deletions

- 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 O_2 species
- Apoptosis-
  - Cell cycle check points (stress, viral infections)