Genetics of Cancer
Lecture 34
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
Most of the mutations that contribute to cancer occur in somatic cells - but germ line mutations can also contribute.
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Signal Transduction and Growth Regulation

Cytoplasmic signal transduction proteins

Nuclear proteins
  Growth Factor Genes
Great Targets for Dominant Acting Oncogenes

Secreted Growth factors, e.g. EGF, PDGF

Specific Receptors for Growth factors e.g., RET, EGFR

Cytoplasmic signal transduction proteins

G-proteins, kinases and their targets e.g., RAS, ABL, (RB)

Nuclear proteins

Growth Factor Genes

Transcription factors, e.g., MYC, JUN, FOS
Receptor Tyrosine Kinases (RTKs)
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Ligand-binding site

Ligand binding

Receptor dimerization

Autophosphorylation on tyrosines

ATP

ADP

Phosphotyrosines

Substrate protein

Tyrosine phosphorylation by dimerized RTK
Extracellular Growth factor

Engages with and dimerizes specific receptors on cell surface

Dimerized Receptor activates cascade of molecular events

Machinery for increased cell proliferation is mobilized

Receptor Tyrosine Kinases (RTKs)
Constitutive Activation converts RTKs to Dominant Acting Oncogenes

Genetic alterations leading to Constitutive Activation of RTKs

- Deletion of extracellular domain
- Mutations that stimulate dimerization without ligand binding
- Mutations of Kinase domain
- Overexpression of Ligand
- Overexpression of Receptor
Two Classic Examples

Her2 receptor

EGF receptor

Her2 = Human Epidermal growth factor receptor 2

EGFR = Epidermal growth factor receptor
EGF Receptors signal through the RAS G-protein

1. Binding of hormone causes dimerization and phosphorylation of cytosolic receptor tyrosine residues
2. Binding of GRB2 and Sos couples receptor to inactive Ras
3. Sos promotes dissociation of GDP from Ras; GTP binds and active Ras dissociates from Sos
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cABL - A non-receptor, cytoplasmic tyrosine kinase that can be converted into an oncoprotein

- cABL proto-oncogene product signals to many of the same molecules as the RTKs

- Signals cell cycle progression and cell proliferation
The Philadelphia Chromosome and Chronic Myeloid Leukemia
Human Chromosome Spread – G-banding Karyotype
Human Chromosome Spread - G-banding Karyotype

Normal
The Philadelphia Chromosome created by a Translocation between Chrs 9 and 22

Chronic Myeloid Leukemia
The Philadelphia Chromosome and Chronic Myeloid Leukemia
The Philadelphia Chromosome and Chronic Myeloid Leukemia
Fusion Protein

Uncontrolled ABL Kinase Activity and Signal Transduction

Chronic Myeloid Leukemia
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Burkitt’s Lymphoma: A chromosome translocation
\[ \rightarrow \text{cMYC to be expressed inappropriately in B-cells} \]

cMYC drives cells from G1 to S
Another way that oncogenic transcription factors can be up-regulated: *Gene Amplification*

Chromosome from a TUMOR

**Blue** - staining of all chromosomes

**Red** - staining of chromosome 4

**Green** - staining of the N-MYC gene

(N-MYC and cMYC share many similar properties)
One more example - with an interesting twist
A translocation between Chr 14 and Chr 18 to put the BCL2 gene under the strong IgH promoter

The BCL2 protein PREVENTS programmed cell death, B cells live longer than normal leading to B-cell Lymphomas
What chromosomal events convert proto-oncogenes to dominantly acting oncogenes

- Point mutations (e.g., RAS)
- 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., Bcl2)
- Gene amplification resulting in overexpression (e.g., N-Myc)
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Cytoplasmic signal transduction proteins
RB – the Retinoblastoma Gene – was the first example of a Tumor Repressor Gene (aka a Recessive Oncogene)

Loss of Function Mutations in both RB genes lead to malignant tumors of the retina during the first few years of life
RB prevents cells from leaving G1 to enter S-phase, until the appropriate time.
Phosphorylation of RB at the **appropriate** time in G1 allows release of the E2F Transcription Factor.

Must lose function of both RB alleles in order to lose cell cycle control.

Transcribes genes for replication and cell proliferation.
Two ways to get retinal tumors due to loss of RB function

Mendelian

Sporadic

Germline mutation

Somatic mutation

Multiple tumors
Bilateral
Early-onset

Normal gene

Somatic mutation
Somatic mutation

Single tumors
Unilateral
Later-onset
The Retinoblastoma disease behaves as an autosomal **dominant** mutation

- In order to lose cell cycle control MUST lose function of both alleles

- But, for Mendelian inheritance of RB, children need only inherit only one non-functional allele

- To explain this the “TWO HIT” hypothesis was proposed

- During development of the retina a second mutation is almost certain to occur

- RB is one of the very few cancers that seems to require defects in only one gene (but in both alleles
How is the second RB allele rendered non-functional?

Loss of Heterozygosity (LOH)

This can happen is several ways:

Heterozygous for RB mutation

Mutant RB
Point Mutation

Non-Disjunction

Chromosome loss & duplication

Chromosome loss

Recombination

Deletion

Interchromosomal Recombination

Translocation

Gene Conversion
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