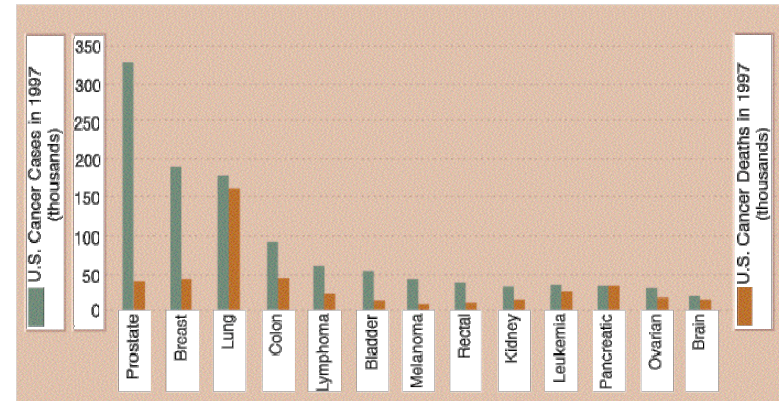


Genetics of Cancer

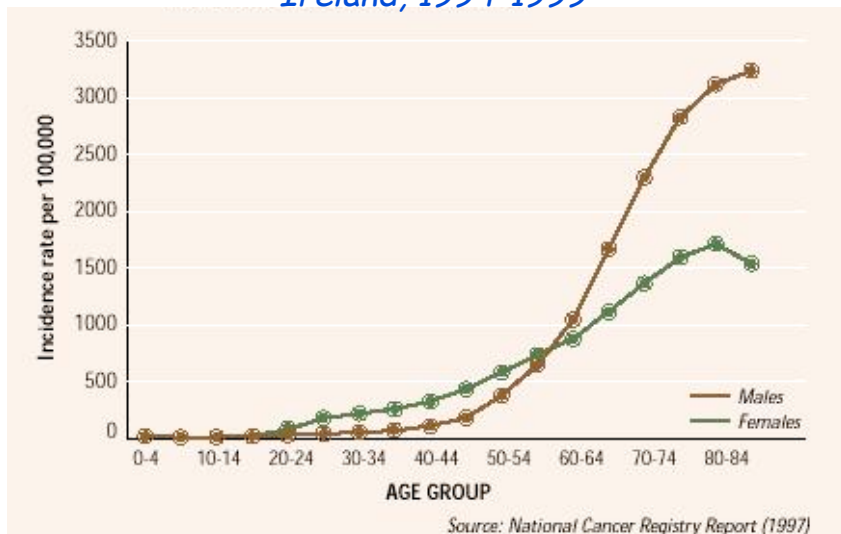
Lecture 32

The Estimated Numbers of New Cancer Cases and Deaths



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Age Specific Cancer Rates: Males and Females, Ireland, 1994-1999

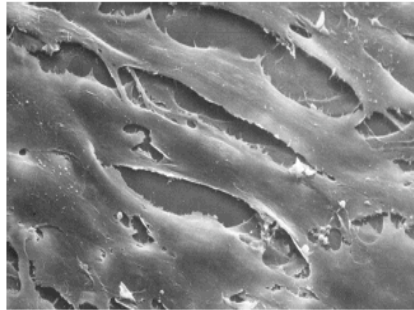


Properties of Cancer Cells

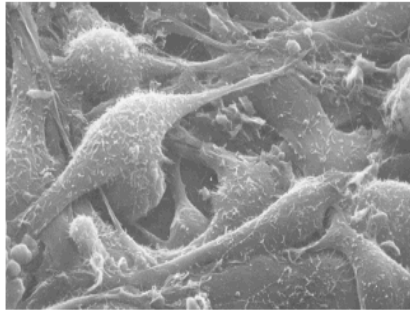
- Loss of Contact inhibition
- Anchorage independent growth
- Can grow indefinitely
- Can grow with low levels of serum growth factors

What do cancer cells look like?

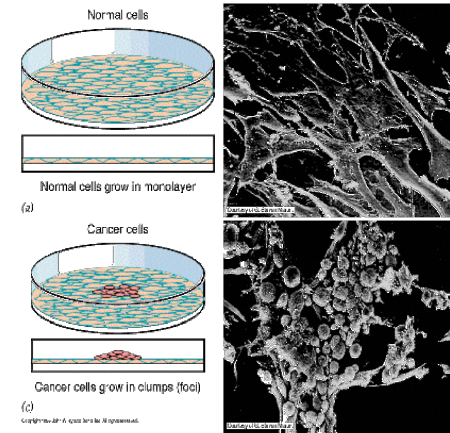
3T3 cells in culture



Transformed 3T3 cells



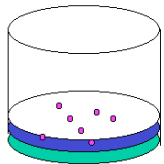
Loss of Contact Inhibition in Cancer Cells



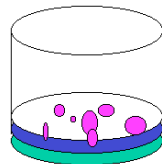
<http://140.116.60.1/mdlai/Handout/cancer-medicine-2000/img009.GIF>

Anchorage Independence

Normal cells cannot grow in soft agar, exist in single cell



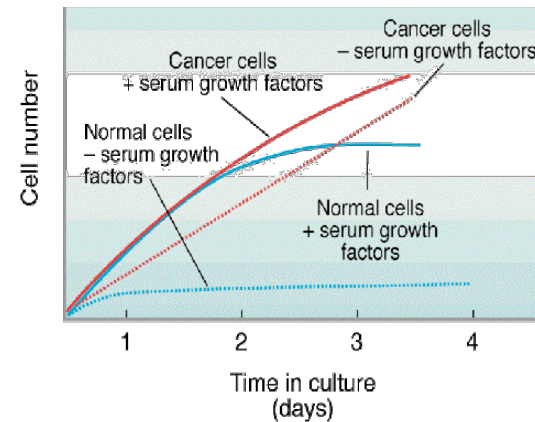
Transformed cells can proliferate and form colonies in soft agar



0.6% agar
0.3% agar

<http://140.116.60.1/mdlai/Handout/cancer-medicine-2000/img009.GIF>

Cancer Cells Can Proliferate With Serum Deprivation

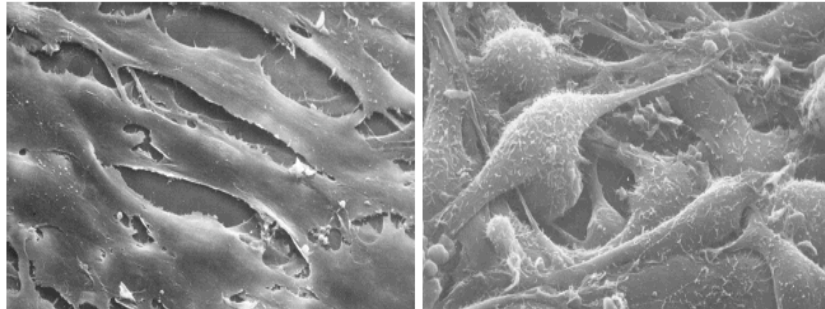


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What do cancer cells look like?

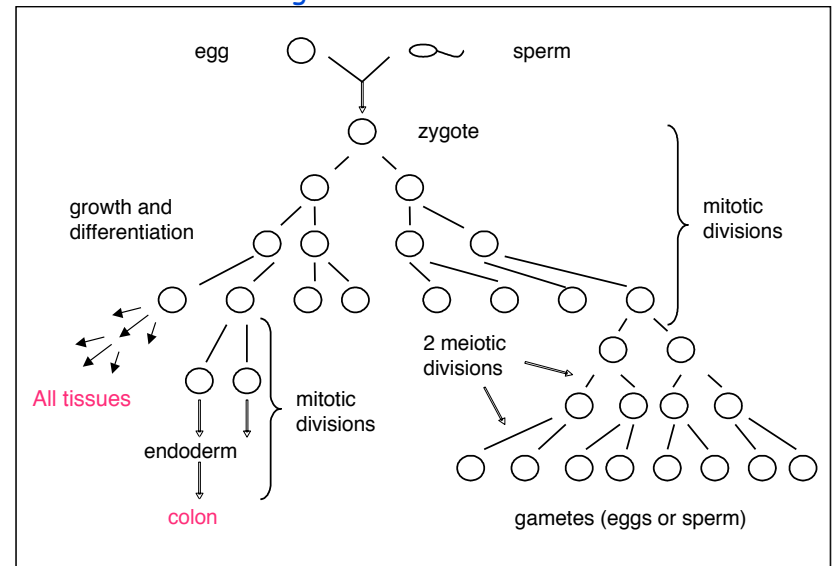
3T3 cells in culture

Transformed 3T3 cells

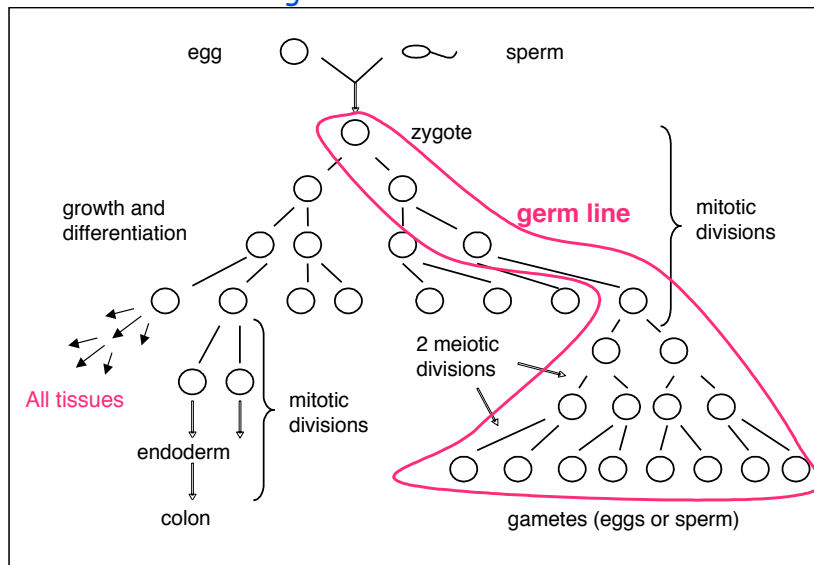


Where do they come from?

Most of the mutations that contribute to cancer occur in somatic cells - but germ line mutations can also contribute



Most of the mutations that contribute to cancer occur in somatic cells - but germ line mutations can also contribute



The Genetic Basis of Cancer and Theodor Boveri 1862 - 1915



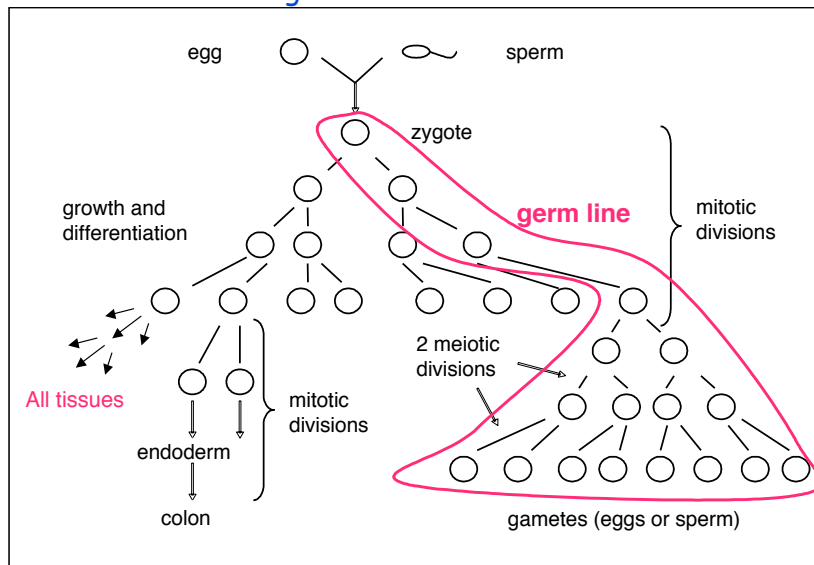
- Established that chromosomes carry the hereditary information by showing that aberrant segregation of chromosomes leads to certain phenotypes in sea urchin eggs.
- Suggested that aberrant segregation of human chromosomes could be responsible for a normal cell becoming a tumor cell
- Suggested that some chromosomes promoted cell growth and others inhibit cell growth

Marcella O'Grady Boveri (1863-1950) also contributed

Major complications in understanding the genetic basis of cancer

- Multiple mutations are necessary to produce a tumor cell
- Different types of tumor have different genes mutated
- Early initiating events occur rarely in complex tissues and are therefore extremely difficult to detect
- The key initiating event often leads to an increase in mutation rate thus tumor cells often bear many fortuitous mutations

Most of the mutations that contribute to cancer occur in somatic cells - but germ line mutations can also contribute



Alterations in different kinds of Genes cause Cancer

Oncogenes

dominant gain-of-function mutations
promote cell transformation

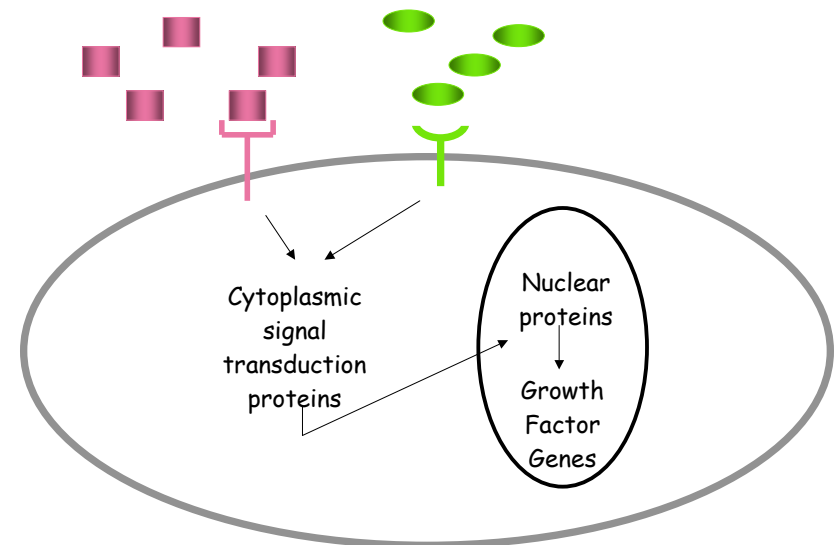
Tumor suppressor genes

recessive, loss-of-function mutations
promote cell transformation

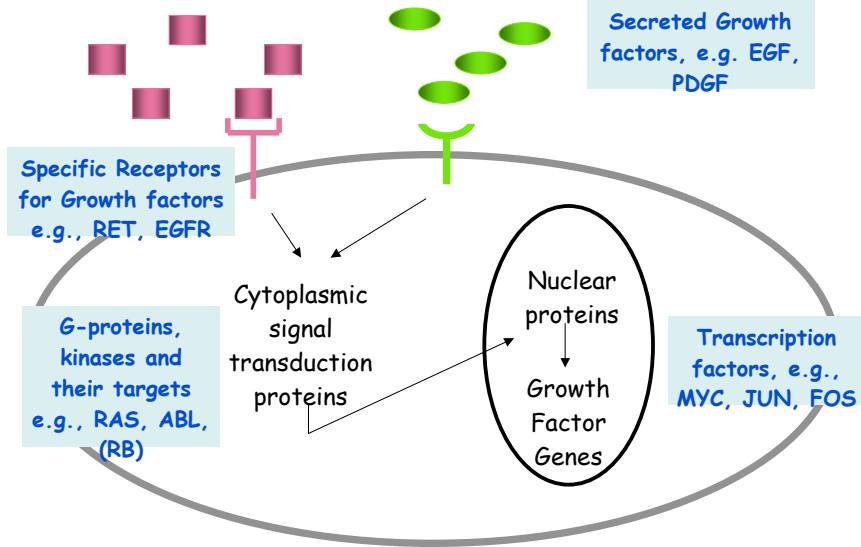
Mutator genes

Usually recessive, loss-of-function mutations
that increase spontaneous and environmentally

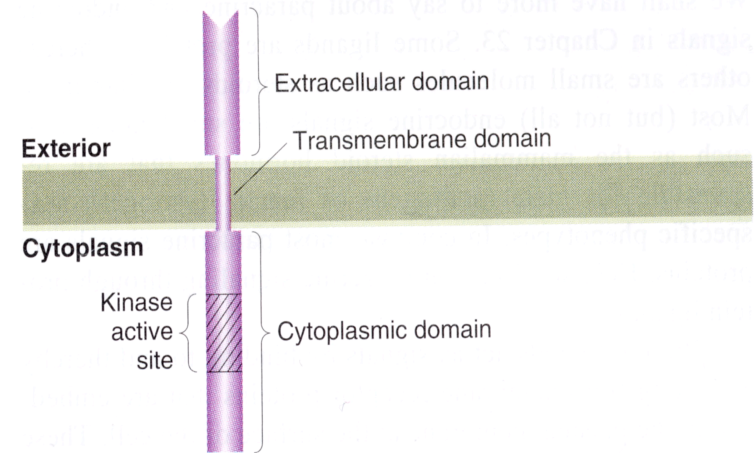
Signal Transduction and Growth Regulation



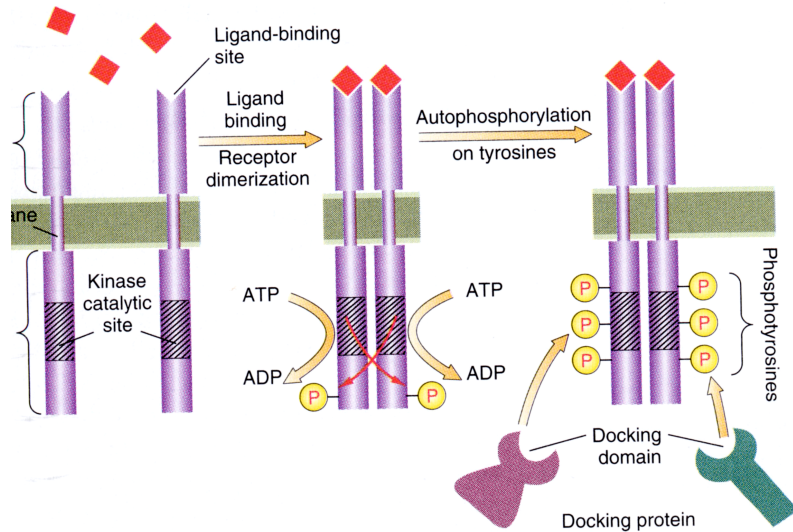
Great Targets for Dominant Acting Oncogenes



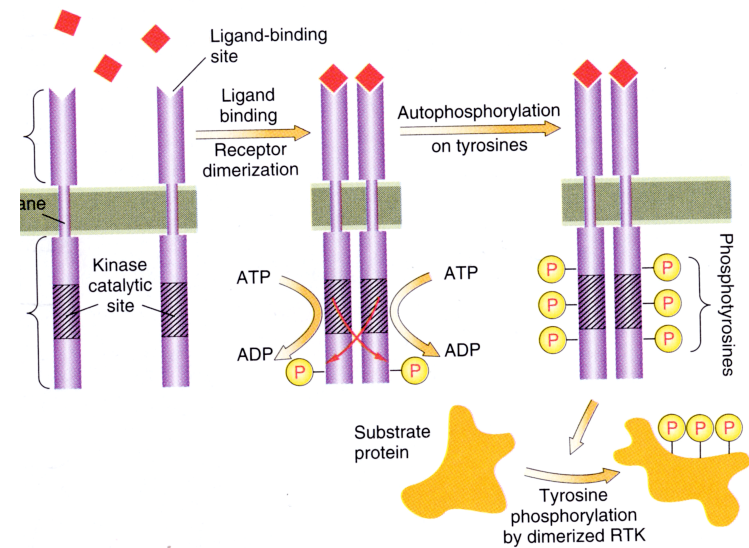
Receptor Tyrosine Kinases (RTKs)

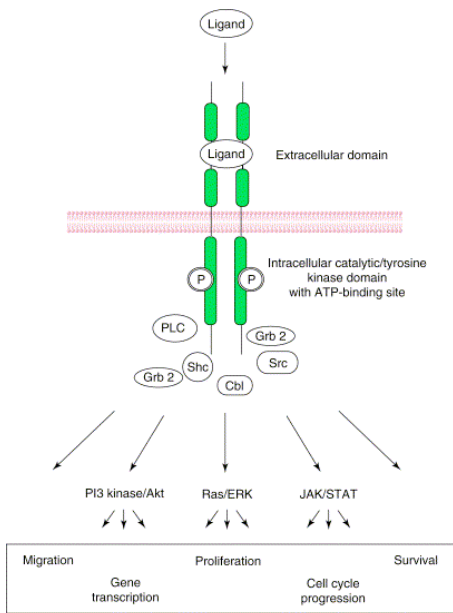


Receptor Tyrosine Kinases (RTKs)



Receptor Tyrosine Kinases (RTKs)

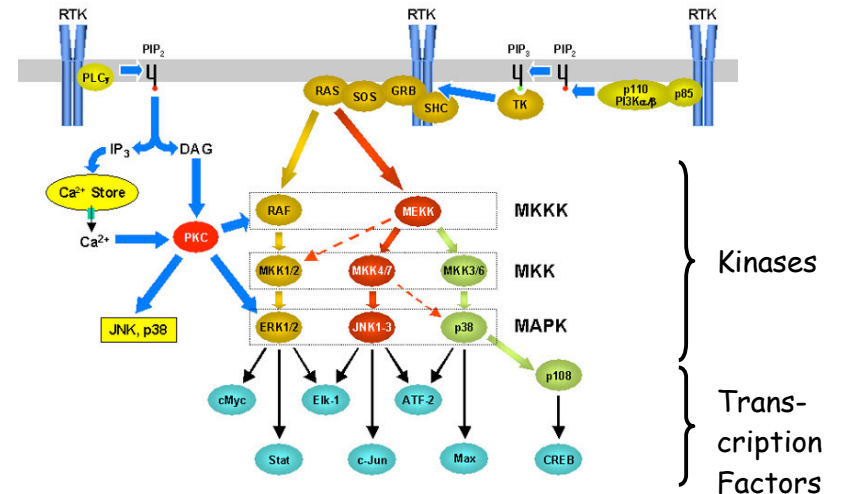




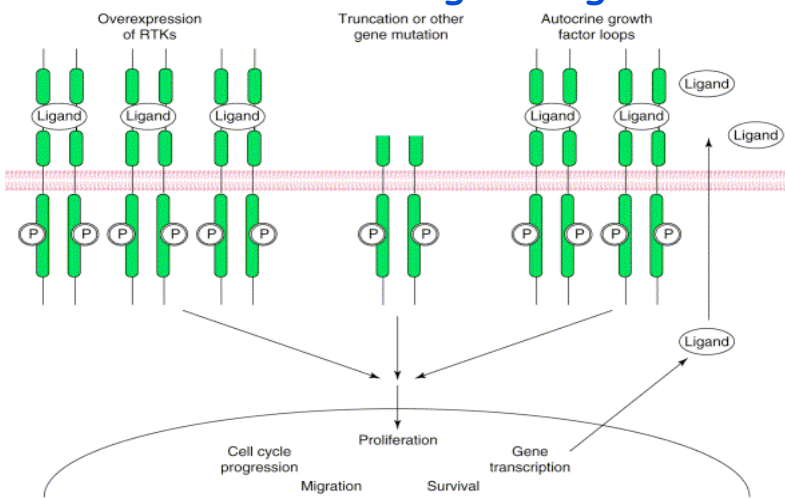
Zwick et al, (2002) TIMM 8:17-23 *TRENDS in Molecular Medicine*

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

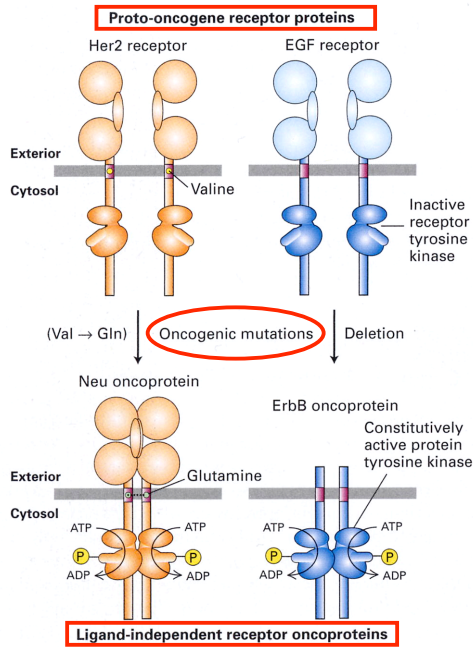


Zwick et al, (2002) TIMM 8:17-23

TRENDS in Molecular Medicine

Genetic alterations leading to Constitutive Activation of RTKs

- Deletion of extracellular domain
- Mutations that stimulate dimerization without ligand binding
- Mutations of the kinase domain
- Overexpression of Ligand
- Overexpression of Receptor



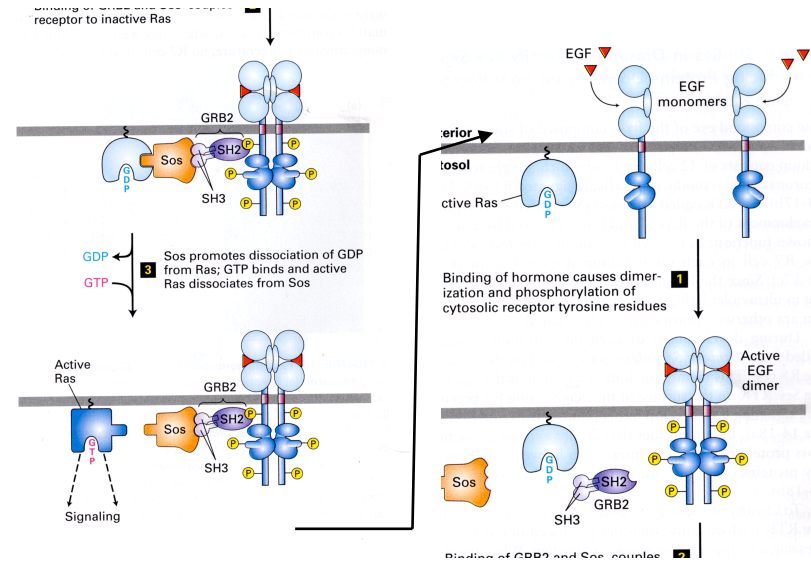
Two Classic Examples

Her2 receptor

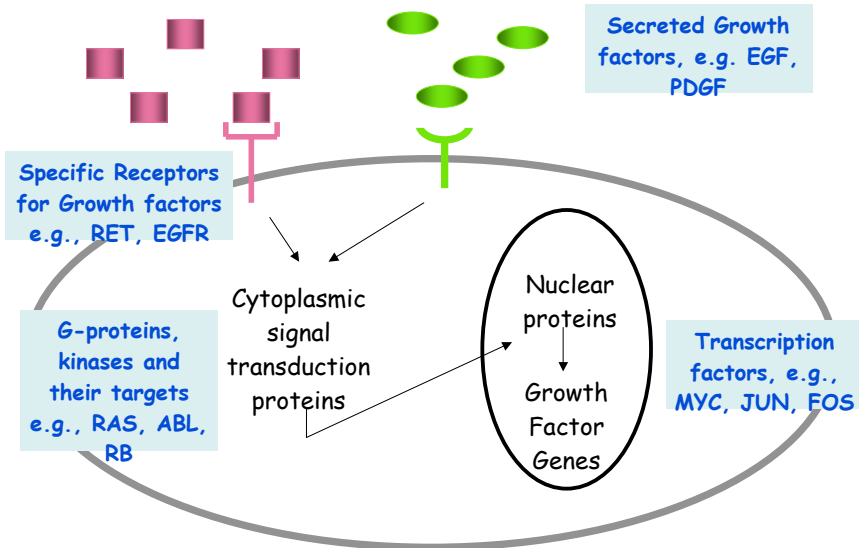
EGF receptor

Her2 = Human Epidermal growth factor receptor 2
 EGFR = Epidermal growth factor receptor

EGF Receptors signal through the RAS G-protein



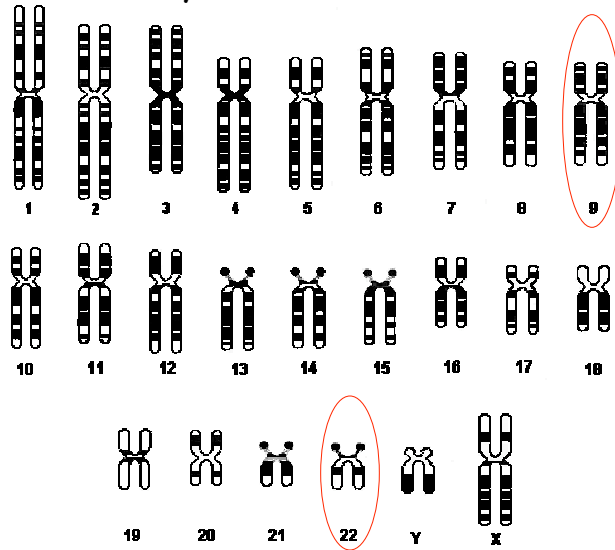
Signal Transduction and Growth Regulation



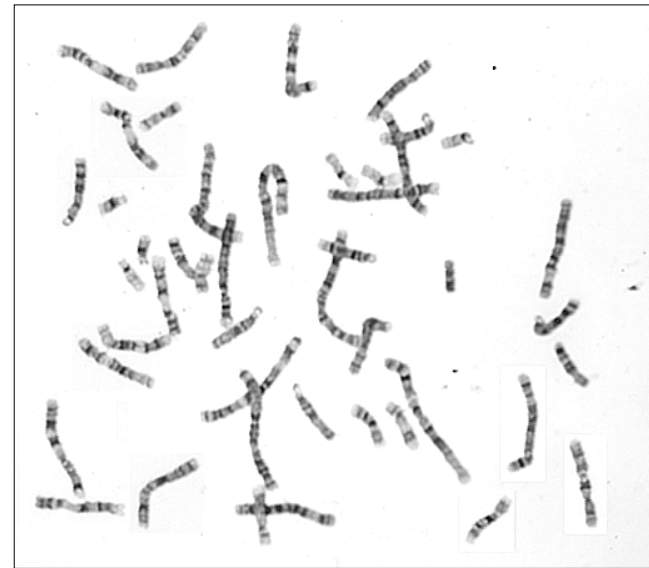
cABL - A non-receptor, cytoplasmic tyrosine kinase that can be converted into an oncoprotein

- cABL proto-oncogene product signals to many of the same molecules as the RTKs
- Signals cell cycle progression and cell proliferation

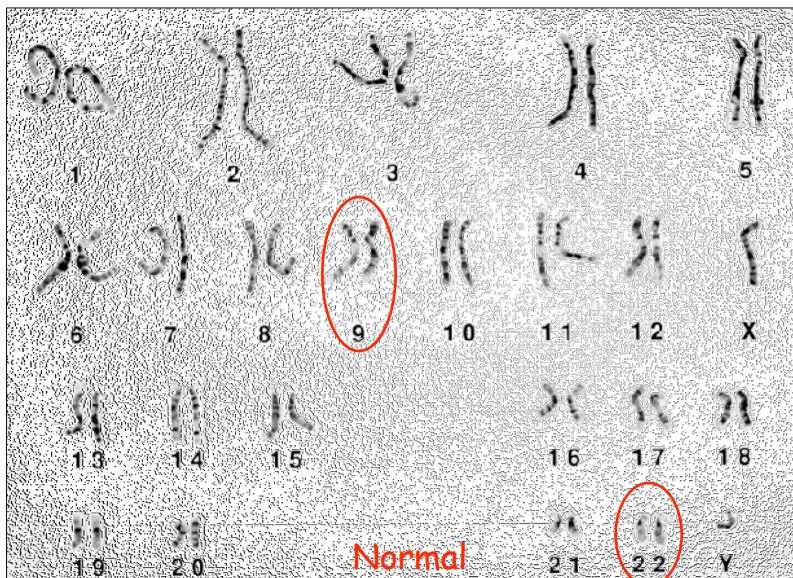
The Philadelphia Chromosome and Chronic Myeloid Leukemia



Human Chromosome Spread - G-banding Karyotype



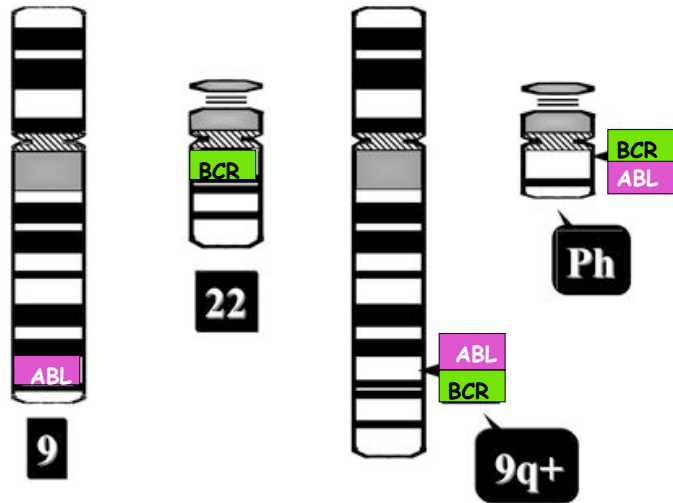
Human Chromosome Spread - G-banding Karyotype



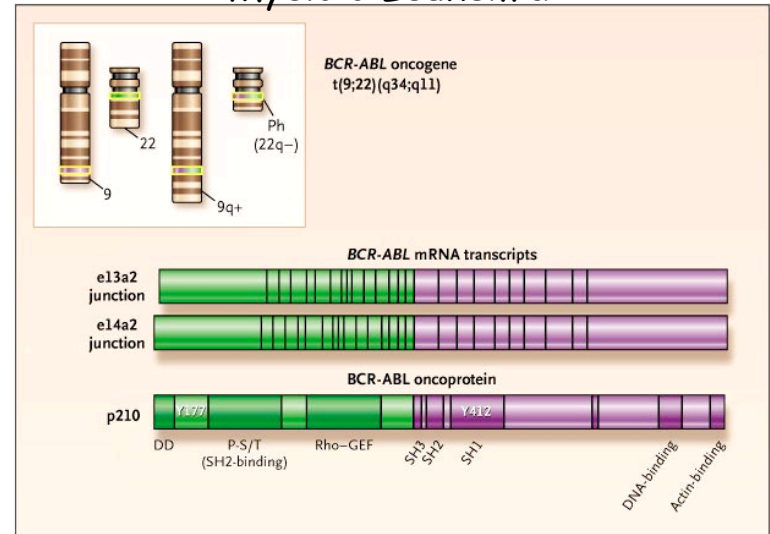
The Philadelphia Chromosome created by a Translocation between Chrs 9 and 22 → Chronic Myeloid Leukemia



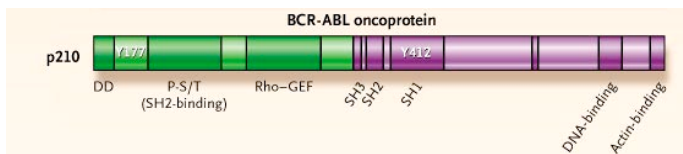
The Philadelphia Chromosome and Chronic Myeloid Leukemia



The Philadelphia Chromosome and Chronic Myeloid Leukemia

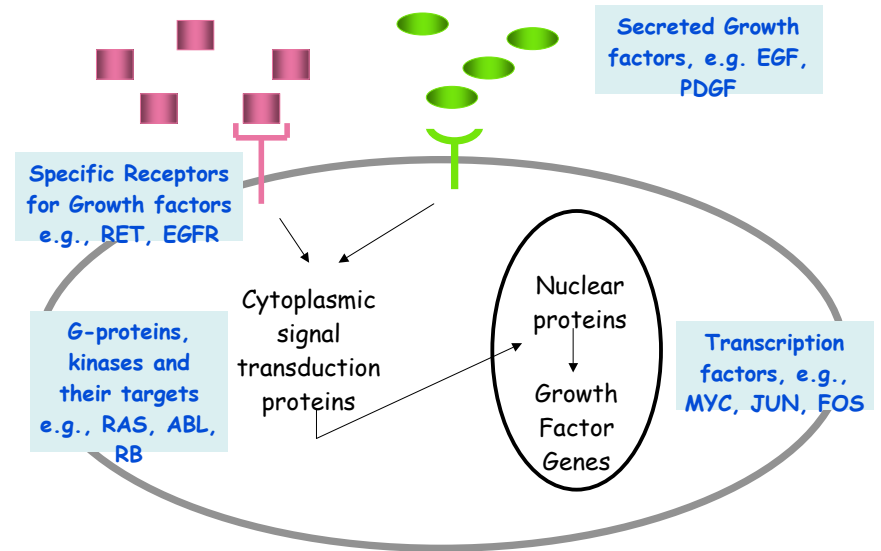


Fusion Protein



Uncontrolled ABL Kinase Activity
and Signal Transduction
Chronic Myeloid Leukemia

Signal Transduction and Growth Regulation



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