

Cancer

The fundamental defect is

unregulated cell division.

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Properties of Cancerous Cells

Altered growth and proliferation

Loss of growth factor dependence

Loss of contact inhibition

Immortalization

Altered cell adhesion (associated with Metastasis)

Poor adhesion, altered CAM expression

Increased ECM proteolysis, lower ECM secretion

Increased membrane transport & radiation resistance

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Causes of Cancer

EM radiation - X-rays, Gamma rays, UV

Chemical carcinogens

Viruses

Insertional mutagenesis

Expression of viral oncogenes

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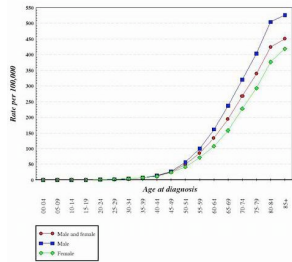
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### "Multiple Hit" Theory of Cancer

Many mutations are required to make a cancerous cell.

Cancer incidence increases with age.



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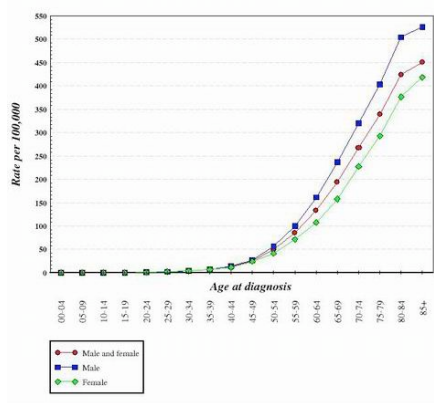
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### Types of Cancer

Carcinomas - epithelial in origin, most common type

Sarcomas - derived from 'connective tissue'

Leukemias and lymphomas - immune cell derived

Teratomas - germ cell derived; rare but fascinating.

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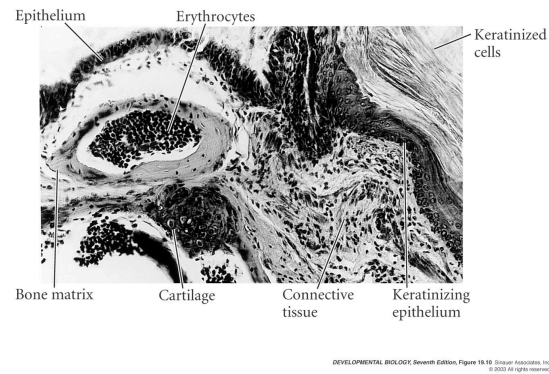
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**Figure 19.10 Photomicrograph of a Section Through a Teratocarcinoma**



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Molecular Genetics of Cancer

Oncogenes

Proto-oncogenes

Tumor Suppressor Genes

Oncogenes - when inappropriately activated or over-expressed, promote unregulated cell division.

Proto-oncogenes - normal cellular versions that can be mutated to become oncogenes

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Molecular Genetics of Cancer

Oncogenes

Proto-oncogenes

Tumor Suppressor Genes

Viral Oncogenes - acquired cellular proto-oncogenes are mutated to permanently activate or over-express

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Molecular Genetics of Cancer

Examples of viral oncogenes

*v-erbB* is a truncated EGF receptor, with permanently activated internal tyrosine kinase domain.

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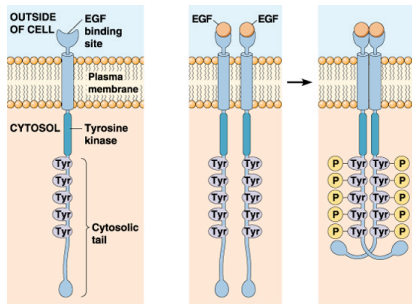
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Normal EGF receptor, with internal tyrosine kinase domain.



(a) Structure of the epidermal growth factor (EGF) receptor

(b) Activation of the EGF receptor

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See also Fig 6.10 in Gilbert

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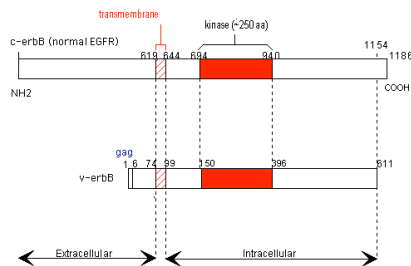
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Molecular Genetics of Cancer

Examples of viral oncogenes:

*v-erbB* is a truncated EGF receptor, with permanently activated internal tyrosine kinase domain.




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Molecular Genetics of Cancer

Examples of viral oncogenes

*v-src* is an intracellular tyrosine kinase (cytoplasmic), also constitutively active.

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Molecular Genetics of Cancer

Normal cellular counterparts of viral oncogenes

*c-erbB* is a normal cellular EGF receptor

*c-src* is cellular intracellular tyrosine kinase, normally activated by a growth factor signaling pathway

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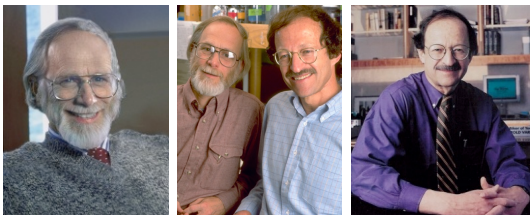
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Molecular Genetics of Cancer

Discovery of viral oncogenes and their origins led to awarding of Nobel Prize (Physiology or Medicine) in 1989 to

J. Michael Bishop & Harold E. Varmus



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Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction pathways

Growth factors

Growth factor receptors

Intracellular signaling proteins

Transcription factors

(Regulators of apoptosis)

(Cell cycle regulators)

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Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction pathways

Growth factors/other secreted factors:

*int2* is FGF-like

*wnt1* is *wingless*-like protein, first discovered as an oncogene activated by insertion of mouse mammary tumor virus (MMTV) near normal gene

(trivia: originally called *int1*, for "integration").

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Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction pathways

Growth factors:

Growth factor / other receptors:

*trkA* (NGF receptor)

*erbB* (EGF receptor)

*ptc* (Patched - Shh receptor)

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Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction paths

Growth factors:

Growth factor receptors:

Intracellular signaling proteins:

*ras* - GTP binding protein

*raf* - intracellular ser/thr kinase - acts just downstream of *ras* in RTK pathway

*src* - intracellular tyrosine kinase

*abl* - intracellular tyrosine kinase

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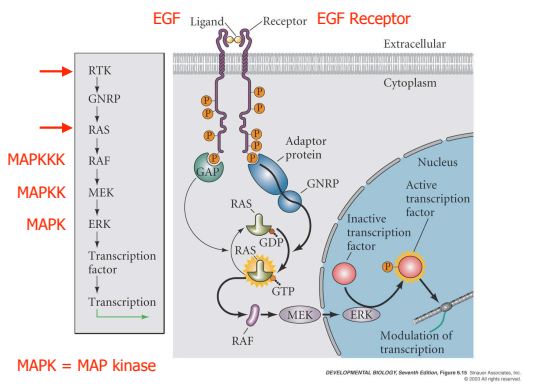
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Molecular Genetics of Cancer: Fig 6.15 - The RTK signal transduction pathway



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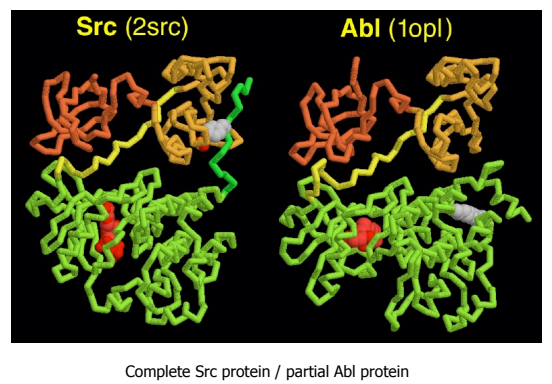
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Molecular Genetics of Cancer - *src* and *abl* intracellular tyr kinases



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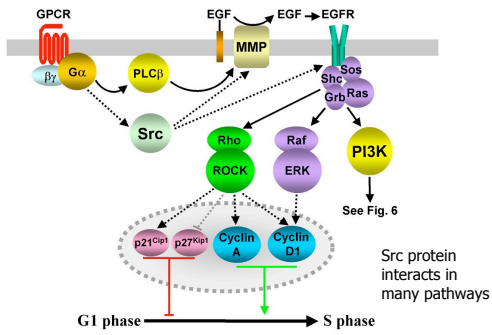
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Molecular Genetics of Cancer - Src functions




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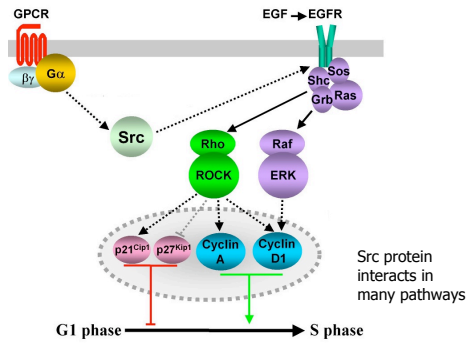
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Molecular Genetics of Cancer - Src functions




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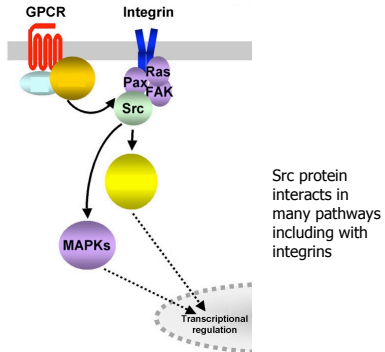
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Molecular Genetics of Cancer - Src functions




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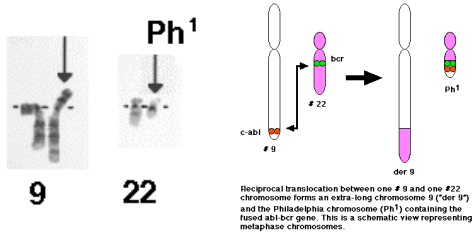
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Molecular Genetics of Cancer

Intracellular signaling proteins:

*abl* - intracellular tyrosine kinase

Causes Chronic Myeloid Leukemia (CML) via novel fusion protein formed by t(9:22) translocation



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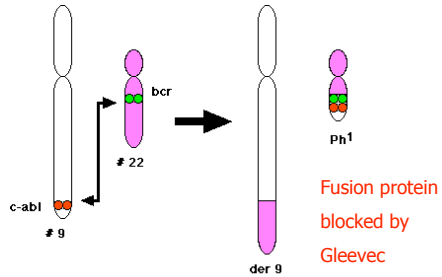
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Molecular Genetics of Cancer

t(9:22) translocation - the "Philadelphia chromosome"



Reciprocal translocation between one # 9 and one #22 chromosome forms an extra-long chromosome 9 ("der 9") and the Philadelphia chromosome (Ph<sup>1</sup>) containing the fused *abl-bcr* gene. This is a schematic view representing metaphase chromosomes.

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Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction pathways

Growth factors:

Growth factor receptors:

Intracellular signaling proteins:

Transcription factors:

*myc* - basic Helix-loop-helix (bHLH)

*fos*, *jun* - basic Leucine zipper (bZIP), together form AP1

$\beta$ -catenin - Wnt signaling pathway TF (can promote transcription from *myc* gene)

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Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction paths

Growth factors:

Growth factor receptors:

Intracellular signaling proteins:

Transcription factors:

Regulators of apoptosis:

*bcl-2*

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Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction paths

Growth factors: *wnt-1, int-2*

Growth factor receptors: *trkA, erbB, ptc*

Intracellular signaling proteins: *ras, raf, src, abl*

Transcription factors: *myc, fos, jun,  $\beta$ -catenin*

Regulators of apoptosis: *bcl-2*

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Molecular Genetics of Cancer

Tumor Suppressor Genes

- normally function to inhibit cell proliferation  
(or promote apoptosis)

- loss-of-function mutations promotes cancer (recessive)

- both copies of tumor suppressor gene must be lost for complete loss-of-function ('2 hit' process)

- inherited mutation in one allele means only single loss of remaining good allele can promote cancer ('LOH')

**The p53 gene** - mutated in ~50% of all human cancers  
(non-heritable, somatic mutations)

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Molecular Genetics of Cancer

Heritable p53 gene mutation causes high cancer risk.

Li Fraumeni syndrome

- rare genetic condition resulting in high cancer rate  
(soft tissue sarcomas, breast cancer, leukemia, brain tumors, melanoma, etc.)  
(50% of patients have cancer by age 40, 90% by age 60)
- mainly caused by missense mutations changing single AA, but also simple deletions
- some mutations create dominant-negative protein (blocks function of normal, wild-type p53 protein)

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Molecular Genetics of Cancer - Tumor Suppressor Genes

p53 protein

- regulates progression through the cell cycle, especially at the G1-S checkpoint.
- blocks entry into S phase if DNA is damaged, allowing time for repair
- if repair fails, then p53 promotes apoptosis

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Molecular Genetics of Cancer - Tumor Suppressor Genes

p53 protein

- is a transcription factor



p53 core DNA-binding domain + DNA  
Yellow - most commonly mutated aa's in human cancer  
Red - Zn ion

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### p53 protein

- is a transcription factor
- turns on p21 (aka WAF1, CIP1) - a **cyclin-dependent kinase inhibitor**
- p21 blocks activity of cyclinE-cdk2 (among others), the main regulator of entry into S phase.

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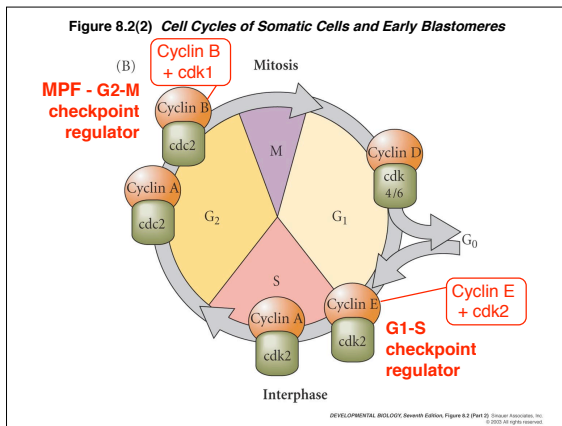
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- if repair fails, then p53 promotes apoptosis

### p53 can

- activate bax gene (pro-apoptotic)
- repress bcl-2 gene (anti-apoptotic)

p53's apoptotic function is, however, largely non-transcriptional (not well understood).

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Molecular Genetics of Cancer - Tumor Suppressor Genes

Other cdk inhibitors are needed:

p16 (Ink4a) is also a cdk inhibitor (especially cdk4),  
is mutated in malignant melanomas

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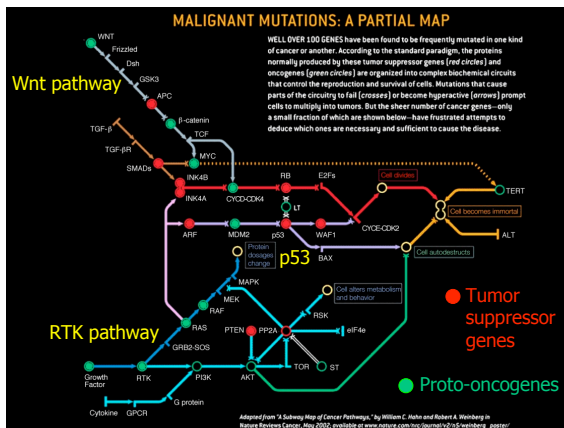
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