Cancer

The fundamental defect is

unregulated cell division.

Properties of Cancerous Cells

Altered growth and proliferation

- Loss of growth factor dependence
- Loss of contact inhibition
- Immortalization

Alterated cell adhesion (associated with Metastasis)

- Poor adhesion, altered CAM expression
- Increased ECM proteolysis, lower ECM secretion

Increased membrane transport & radiation resistance

Causes of Cancer

EM radiation - X-rays, Gamma rays, UV

Chemical carcinogens

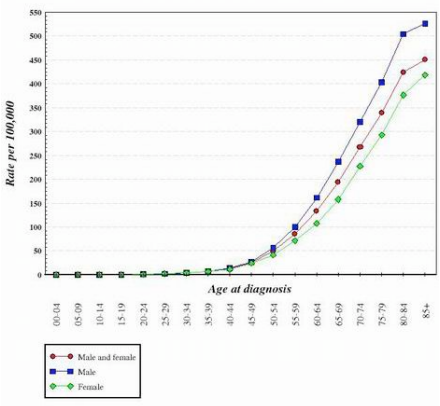
Viruses

- Insertional mutagenesis
- Expression of viral oncogenes

"Multiple Hit" Theory of Cancer

Many mutations are required to make a cancerous cell.

Cancer incidence increases with age.



Types of Cancer

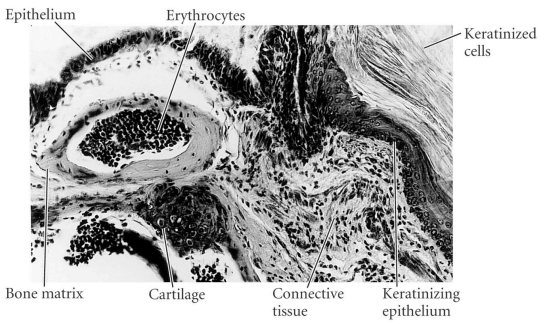
Carcinomas - epithelial in origin, most common type

Sarcomas - derived from 'connective tissue'

Leukemias and lymphomas - immune cell derived

Teratomas - germ cell derived; rare but fascinating.

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



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

Molecular Genetics of Cancer

Oncogenes

Proto-oncogenes

Tumor Suppressor Genes

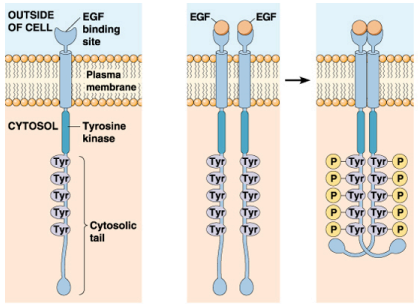
Viral Oncogenes - acquired cellular proto-oncogenes are mutated to permanently activate or over-express

Molecular Genetics of Cancer

Examples of viral oncogenes

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

Normal EGF receptor, with internal tyrosine kinase domain.

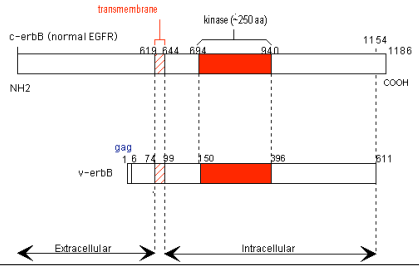


See also Fig 6.10 in Gilbert

Molecular Genetics of Cancer

Examples of viral oncogenes:

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



Molecular Genetics of Cancer

Examples of viral oncogenes

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

Molecular Genetics of Cancer

Normal cellular counterparts of viral oncogenes

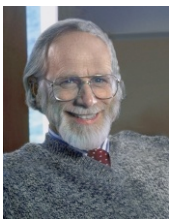
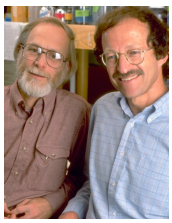
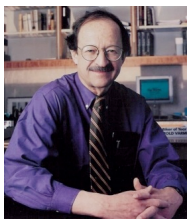
c-erbB is a normal cellular EGF receptor

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

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

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)

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").

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)

Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction paths

Growth factors:

Growth factor receptors:

Intracellular signaling proteins:

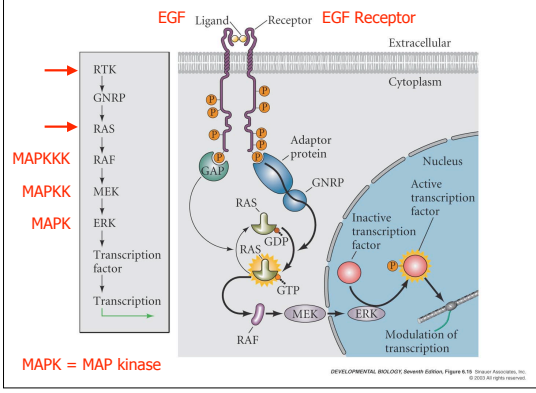
ras - GTP binding protein

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

src - intracellular tyrosine kinase

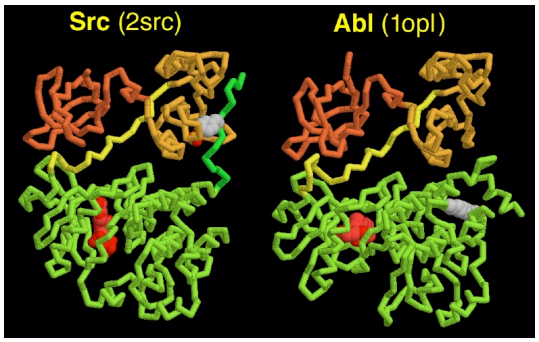
abl - intracellular tyrosine kinase

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



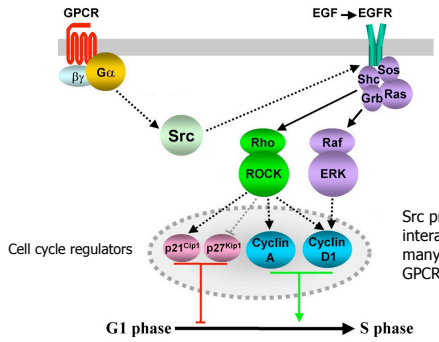
MAPK = MAP kinase

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



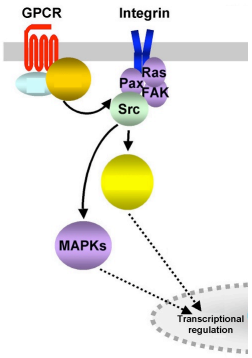
Complete Src protein / partial Abl protein

Molecular Genetics of Cancer - Src functions



Src protein interacts in many pathways: GPCRs, RTK

Molecular Genetics of Cancer - Src functions



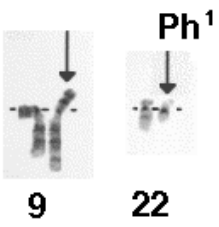
Src protein interacts in many pathways including with integrins

Molecular Genetics of Cancer

Intracellular signaling proteins:

abl - intracellular tyrosine kinase

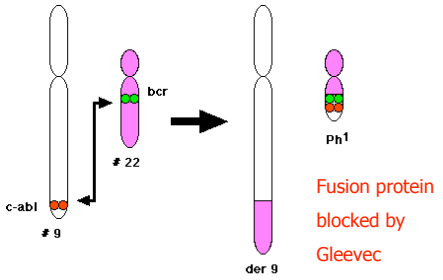
Causes Chronic Myeloid Leukemia (CML) via novel fusion protein formed by t(9:22) translocation



Karyotype of t(9:22) reciprocal translocation causing CML

Molecular Genetics of Cancer

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



Fusion protein blocked by Gleevec

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

Molecular Genetics of Cancer

Many proto-oncogenes are in signal transduction pathways

Growth factors:

Growth factor receptors:

Intracellular signaling proteins:

Transcription factors:

β-catenin - Wnt signaling pathway TF

myc - basic Helix-loop-helix (bHLH) - can be turned by Wnt pathway (directly by β-catenin + TCF)

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

Figure 6.24(1) ***The Wnt Signal Transduction Pathway***

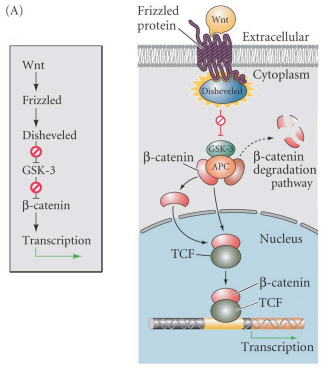
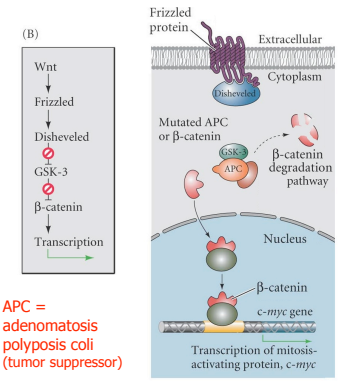


Figure 6.24(2) ***The Wnt Signal Transduction Pathway***

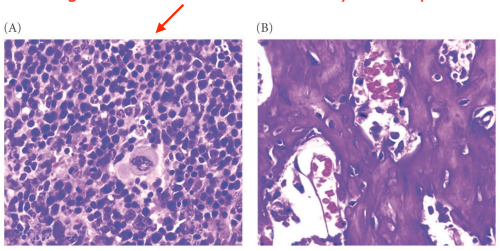


APC = adenomatosis polyposis coli (tumor suppressor)

Activated Wnt pathway turns on *myc* gene

Figure 21.18 ***Differentiation of Osteogenic Sarcomas in Mice Due to Inactivation of the Myc Transcription Factor***

Osteogenic sarcoma associated with *myc* overexpression



Differentiation induced by blocking *myc* expression

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

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, β-catenin*

Regulators of apoptosis: *bcl-2*

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)

Molecular Genetics of Cancer

Heritable p53 gene mutation causes high cancer risk.

Li Fraumeni syndrome

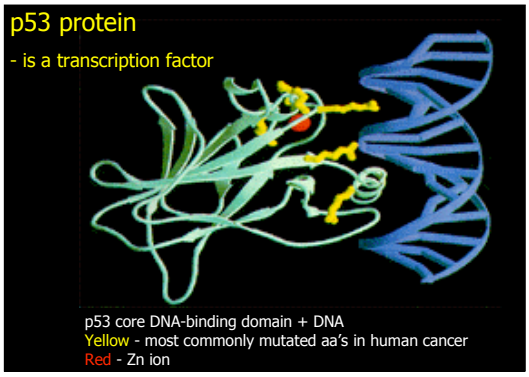
- rare genetic condition resulting in high cancer rate
  (soft tissue sarcomas, breast cancer, leukemia, brain tumors, melanoma, etc.)
  (50% of patients have cancer by age 40, 90% by age 60)
- mainly caused by missense mutations changing single AA, but also simple deletions
- some mutations create dominant-negative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

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

p53 protein

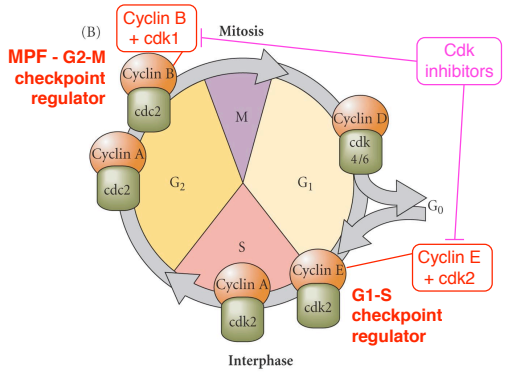
- is a transcription factor



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.

Figure 8.2(2) *Cell Cycles of Somatic Cells and Early Blastomeres*



Molecular Genetics of Cancer - Tumor Suppressor Genes

- 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).

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

Molecular Genetics of Cancer - Cancer Genomics

Hundreds of tumors can be tested for hundreds of genes

Vol 455|23 October 2008|doi:10.1038/nature07423 nature

ARTICLES

Somatic mutations affect key pathways in lung adenocarcinoma

Li Ding[1]*, Gad Getz[2]*, David A. Wheeler[3]*, Elaine R. Mardis[1], Michael D. McLellan[1], Kristian Cibulskis[2], Carrie Sougnez[2], Heidi Greulich[2,4], Donna M. Muzny[3], Margaret B. Morgan[3], Lucinda Fulton[1], Robert S. Fulton[1], Qunyuan Zhang[3], Michael C. Wendl[1], Michael S. Lawrence[2], David E. Larson[1], Ken Chen[1], David J. Dooling[1], Aniko Sabo[3], Alicia C. Hawes[3], Hua Shen[3], Shalini N. Jhangiani[3], Lora R. Lewis[3], Otis Hall[3], Yiming Zhu[3], Tittu Mathew[3], Yanru Ren[3], Jiqiang Yao[3], Steven E. Scherer[3], Kerstin Clerc[3], Ginger A. Metcalf[3], Brian Ng[3], Aleksandar Milosavljevic[3], Manuel L. Gonzalez-Garay[3], John R. Osborne[1], Rick Meyer[1], Xiaoqi Shi[1], Yuzhu Tang[1], Daniel C. Koboldt[1], Ling Lin[1], Rachel Abbott[1], Tracie L. Miner[1], Craig Pohl[1], Ginger Fewell[1], Carrie Haipek[1], Heather Schmidt[1], Brian H. Dunford-Shore[1], Aldi Kraja[1], Seth D. Crosby[1], Christopher S. Sawyer[1], Tammi Vickery[1], Sacha Sander[1], Jody Robinson[1], Wendy Winckler[2,4], Jennifer Baldwin[2], Lucian R. Chirieac[2,5], Amit Dutt[2,4], Tim Fennell[2], Megan Hanna[2,4], Bruce E. Johnson[4], Robert C. Onofrio[2], Roman K. Thomas[6,8], Giovanni Tonon[4], Barbara A. Weir[2,4], Xiaojun Zhao[2,4], Liuda Ziaugra[2], Michael C. Zody[2], Thomas Giordano[10], Mark B. Orringer[11], Jack A. Roth[12], Margaret R. Spitz[13], Ignacio I. Wistuba[12,14], Bradley Ozenberger[15], Peter J. Good[15], Andrew C. Chang[11], David G. Beer[11], Mark A. Watson[16], Marc Ladanyi[17,18], Stephen Broderick[17], Akihiko Yoshizawa[17], William D. Travis[17], William Pao[17,19], Michael A. Province[3], George M. Weinstock[1], Harold E. Varmus[19], Stacey B. Gabriel[2], Eric S. Lander[2], Richard A. Gibbs[3], Matthew Meyerson[2,4] & Richard K. Wilson[1]

Determining the genetic basis of cancer requires comprehensive analyses of large collections of histopathologically well-classified primary tumours. Here we report the results of a collaborative study to discover somatic mutations in 188 human lung adenocarcinomas. DNA sequencing of 623 genes with known or potential relationships to cancer revealed more than 1,000 somatic mutations across the samples. Our analysis identified 26 genes that are mutated at significantly high frequencies and thus are probably involved in carcinogenesis. The frequently mutated genes include tyrosine kinases, among them the *EGFR* homologue *ERBB4*; multiple ephrin receptor genes, notably *EPHA3*; vascular endothelial growth factor receptor *KDR*; and *NTRK* genes. These data provide evidence of somatic mutations in primary lung adenocarcinoma for several tumour suppressor genes involved in other cancers—including *NF1*, *APC*, *RB1* and *ATM*—and for sequence changes in *PTPRD* as well as the frequently deleted gene *LRP1B*. The observed mutational profiles correlate with clinical features, smoking status and DNA repair defects. These results are reinforced by data integration including single nucleotide polymorphism array and gene expression array. Our findings shed further light on several important signalling pathways involved in lung adenocarcinoma, and suggest new molecular targets for treatment.

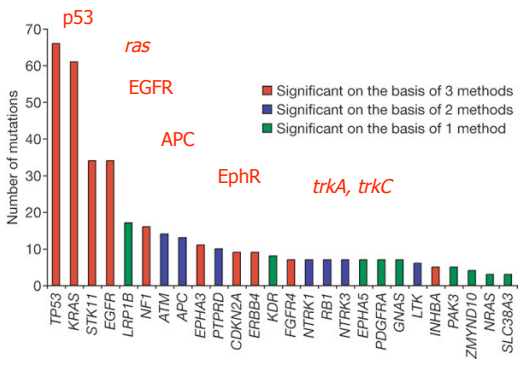
188 tumors

623 genes tested

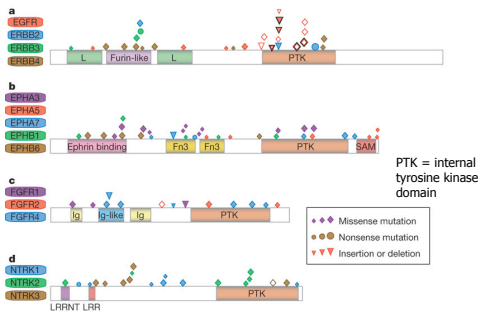
>1000 mutations found

26 genes

Molecular Genetics of Cancer - Cancer Genomics



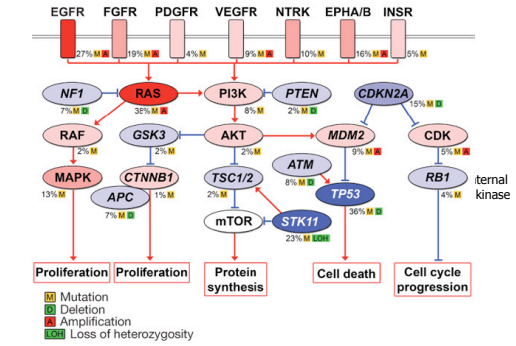
Molecular Genetics of Cancer - Cancer Genomics



PTK = internal tyrosine kinase domain

Receptor Tyrosine Kinases

Molecular Genetics of Cancer - Cancer Genomics



ternal kinase