

Harvey Lodish • Arnold Berk • Chris A. Kaiser •
 Monty Krieger • Matthew P. Scott • Anthony Bretscher •
 Hidde Ploegh • Paul Matsudaira

Molecular Cell Biology

Sixth Edition

Chapter 25: Cancer

Sections 25.1 - 25.5, Osteopontin D.T. Denhardt
 146:470 & 148:514 Dec. 8, 2008

Copyright © 2008 by W. H. Freeman & Company

Section 25.1: Tumor Cells and the Onset of Cancer
Cancer causes about 20% of deaths in the US each year.

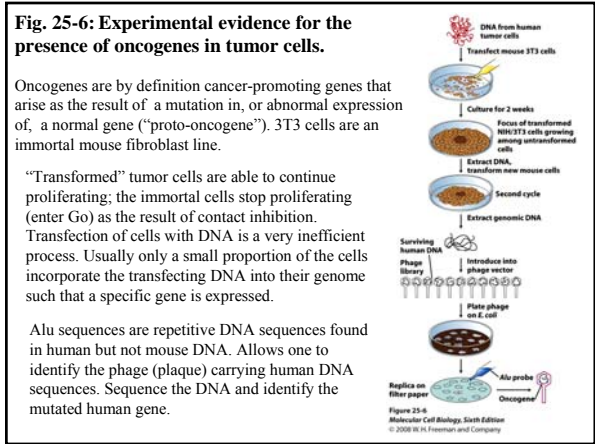
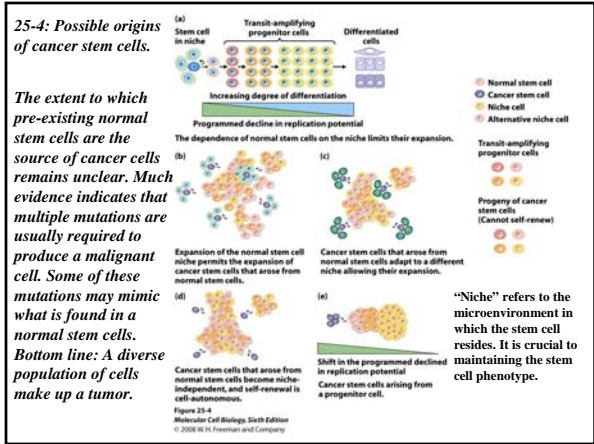
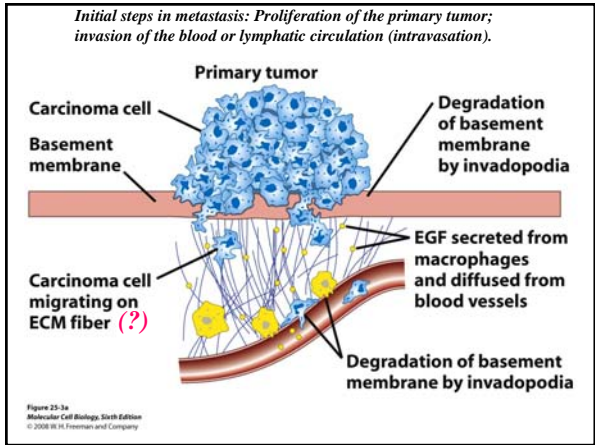
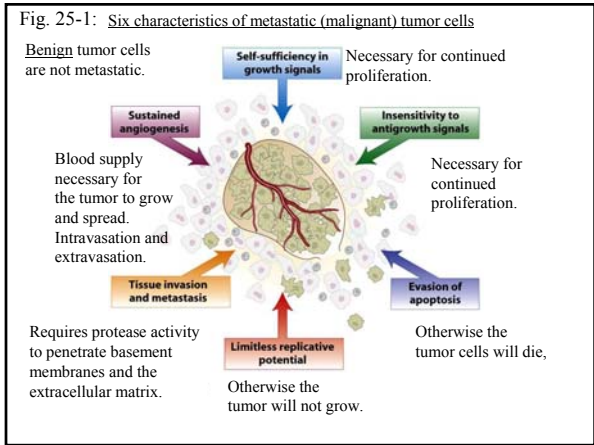
Cancers arise as the result of an interplay between your genetic heritage, the environment, luck, and your choice of lifestyle and occupation.

Older therapies included radiation and chemotherapy; newer therapies entail targeting specific tumors with appropriate drugs, including monoclonal antibodies. Inhibitors (angiostatin, endostatin) of factors (VEGF, FGF, TGF α) inducing angiogenesis hold great promise.

Benign tumors do not spread – warts for example. Malignant tumors (cancers) invade and spread throughout the body (metastasis).

Carcinomas – arise from endoderm (gut) or ectoderm (skin, neural epithelium). Sarcomas – arise from mesodermal tissues (muscle, blood, connective tissue).

Cancers arise more readily in tissues that contain proliferating (stem) cells.



Immortality, as applied to cells, is the property of indefinite cell proliferation. Normal (primary) cells, with the exception of stem cells, have a limited lifetime.

Cancer cells are of necessity, and by definition, immortal cells. But immortal cells, e.g. 3T3 cells, are not necessarily cancer cells. They cannot form tumors in animals.

Various mutations can lead to immortality: for example, a mutation in p16, a CDK inhibitor, allows uncontrolled proliferation when conditions are right (presence of necessary growth factors, absence of contact inhibition). In diploid cells both copies of the p16 gene would have to be mutated. This is a recessive "loss of function" mutation, generally required for tumor suppressors (except when the protein functions as an oligomer).

Additional mutations, e.g. in ras, are required to convert the immortal cell to a cancer cell. Mutations in ras, inhibiting the GTPase activity for example, are constitutively active "gain of function" mutations and are typically dominant.

Fig. 25-7. Cancer incidence typically increases with age because more than one mutation is usually required for a normal cell to become a tumor cell.

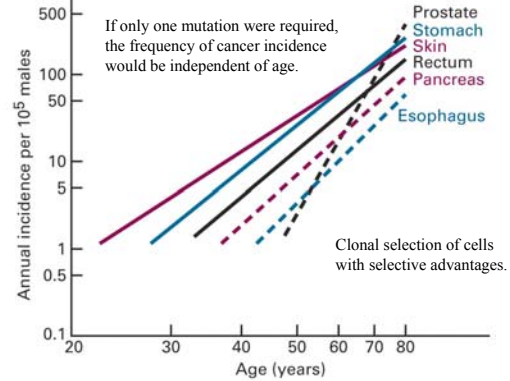


Fig. 25-8: Evidence that oncogenes can cooperate to accelerate tumor development.

Tumor incidence in mice carrying either one or two oncogenic transgenes.

Use of a breast-specific promoter found in the mouse mammary tumor virus to drive oncogene expression in breast tissue.

Ras: signal transduction
Myc: transcription factor

Note the synergistic effect of multiple oncogenes.

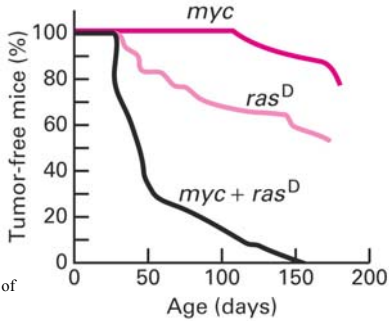
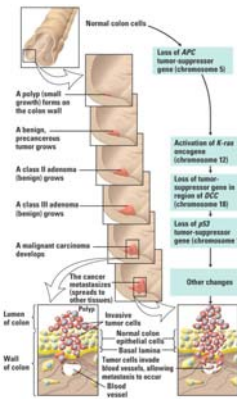


Fig. 25-9. The development and metastasis of human colorectal cancer through well-characterized stages: polyps, benign adenomas, carcinomas.

Multiple mutations in several proto-oncogenes and tumor suppressor genes are generally required, though the order in which the mutations occur is not fixed.

Loss of APC activity (inhibits Wnt signaling) allows uncontrolled proliferation. APC and DCC are tumor suppressor genes.

Popular, and possibly incorrect, current dogma is that "cancer cells usually arise from stem cells". This likely can happen, the argument is how frequently is it the case.



Section 25.2: The Genetic Basis of Cancer

Proto-oncogenes become oncogenes because
1) of a genetic mutation or
2) a chromosomal translocation resulting in gene fusion.
In either case, the protein is altered.

Alternatively, a chromosomal translocation or gene amplification can result in abnormally high expression of the normal protein.

Tumor suppressor genes are usually:

- 1) Negative regulators of the cell cycle (Rb, p16).
- 2) Receptors or signal transducers that inhibit proliferation (TGFbeta).
- 3) Checkpoint mutations controlling cell cycle and apoptosis (p53).
- 4) Proteins involved in DNA repair (mismatch repair, nucleotide excision repair, repair of double-strand breaks – XP, FA, BRCA – Table 25-2.)

Fig. 25-11: Seven types of proteins that participate in controlling cell growth and proliferation.

Mutations in genes encoding proteins I-IV are typically "gain-of-function" mutations that subvert cellular control mechanisms. Cell-cycle and DNA-repair proteins (VI, VII) are typically tumor suppressors ("loss of function"). Apoptotic proteins (V) include tumor suppressors and oncoproteins.

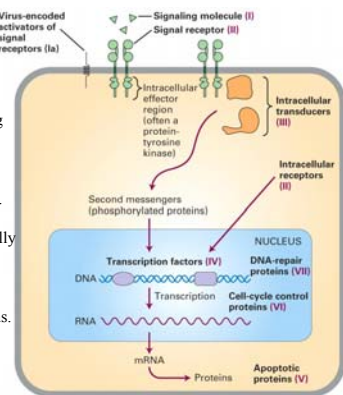
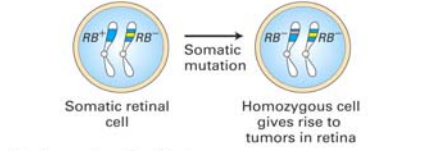
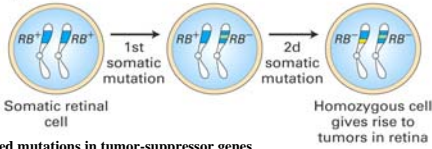


Fig. 25-13: Role of spontaneous somatic mutation in retinoblastoma. This was the first cancer to be shown to result from mutations in a tumor-suppressor gene.

(a) Hereditary retinoblastoma (only 1 mutation now required)



(b) Sporadic retinoblastoma (requires 2 mutations)



Thus inherited mutations in tumor-suppressor genes (e.g. Rb, p53, APC, BRCA1, checkpoint and DNA repair genes) increase cancer risk.

Fig. 25-14. Two mechanisms for loss of heterozygosity (LOH) of tumor-suppressor genes. This allows the recessive allele to become homozygous

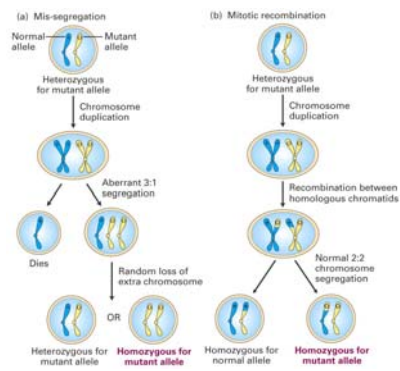
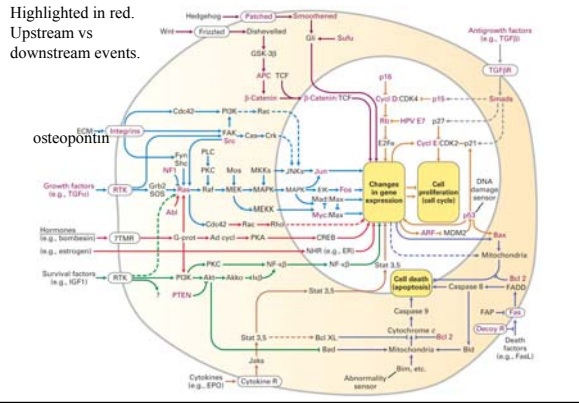


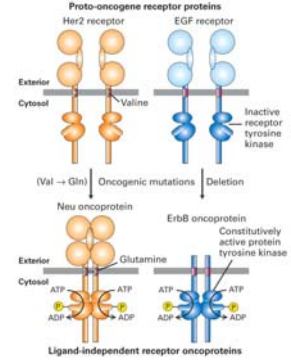
Fig. 25-15: Cell circuitry that is affected by cancer-causing mutations.



Section 25.3 Oncogenic Mutations in Growth-Promoting Proteins

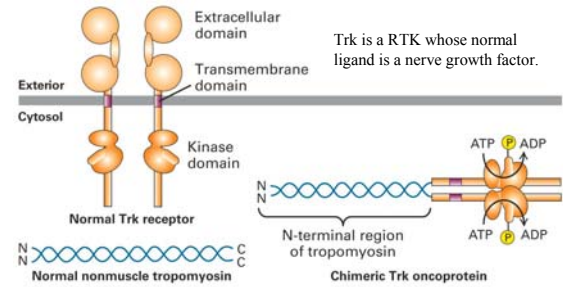
Fig. 25-16: Effect of oncogenic mutations in proto-oncogenes that encode cell surface receptors.

These receptors are often activated by ligand-induced dimerization. Thus any kind of mutation that allows ligand-independent dimerization, or overproduction of the normal receptor, will result in constitutive activation of the signal transduction pathways controlled by that receptor.



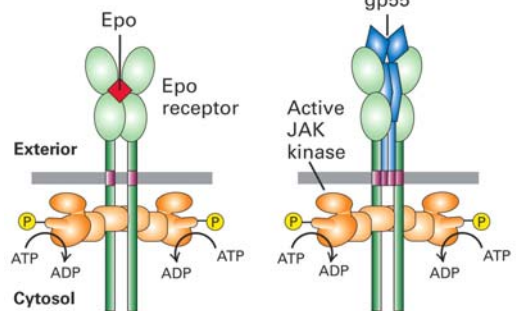
Monoclonal antibody therapies: Herceptin targets Her2, Cetuximab targets the EGFR (When these are over-produced.)

Fig. 25-17: Domain structures of normal tropomyosin, the normal Trk receptor, and a chimeric Trk oncoprotein that resulted from a chromosomal translocation that replaced the extracellular domain of the Trk receptor with a piece of tropomyosin.



Dimerization of Trk results from the ability of tropomyosin to dimerize. Note that the absence of the N-terminal Trk signal sequence targeting the membrane results in a cytosolic localization of the chimeric Trk oncoprotein.

Fig. 25-18: Activation of the erythropoietin (Epo) receptor by the natural ligand, Epo, or a viral oncoprotein produced by the spleen focus-forming virus SFFV.



Epo and gp55 induce erythrocyte formation from erythroid progenitor cells. Subsequent mutations lead to the production of malignant clones.

Src is the founding member of a family of cytosolic non-receptor tyrosine kinases. It was originally identified in the Rous sarcoma virus of chickens, a cancer-inducing virus. They are typically bound to the plasma membrane by an N-terminal myristate.

The src protein contains SH2 and SH3 phosphotyrosine- and proline-rich-peptide-binding domains. A tyrosine (527) near the C-terminus of the src protein binds to the src SH2 domain when it is phosphorylated. This prevents the catalytic protein tyrosine kinase domain of src from functioning.

Dephosphorylation of the "C-terminal" tyrosine phosphate by a phosphatase activated by an upstream signal causes activation of src. This can happen when the src tyrosine phosphate is displaced by a tyrosine phosphate of another protein that has a higher affinity for the SH2 domain; the src tyrosine kinase can now function and the exposed phosphorylated Y is dephosphorylated.

The Abl kinase is another member of the src family. When translocated to the ber locus a gene fusion occurs placing the bcr-abl chimeric protein under the control of the bcr promoter. This forms the "Philadelphia chromosome" that is diagnostic of chronic myelogenous leukemia. Recently a drug was developed, Gleevec, that is a specific inhibitor of the abl kinase and is a cure for CML.

Fig. 25-19a: Structure of the Src tyrosine kinases and activation by an oncogenic mutation. Binding of phosphorylated Y⁵²⁷ to the SH2 domain inhibits the kinase.

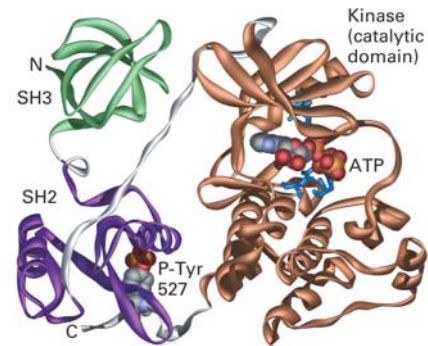
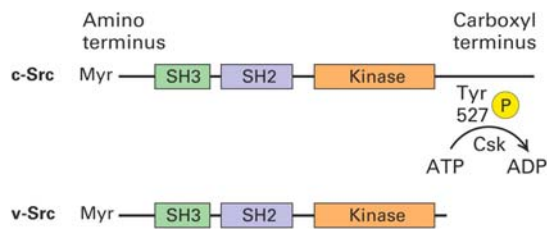


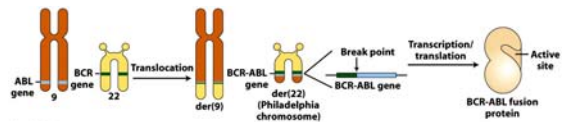
Fig. 25-19b: Domain structure of c-Src and v-Src.



Phosphorylation of Y⁵²⁷ by the C-src kinase CSK inhibits Src activity. If Y⁵²⁷ is not phosphorylated, or missing (C-terminal deletion) as in v-src, then the kinase is constitutively active. Myr represents the myristic acid residue (a 14-carbon fatty acid) coupled to the amino terminus of the protein; it attaches the protein to the lipid bilayer plasma membrane.

Fig. 25-20: Origin of the Bcr-Abl protein kinase.

The translocation of the tip of chromosome 9 to the tip of chromosome 22 forms an abnormal and readily recognizable chromosome known as the Philadelphia chromosome. Hematopoietic cells with this translocation give rise to chronic myelogenous leukemia.



The oncogene arises as the result of the translocation as the result of a chromosomal translocation that fuses a part of the c-abl gene with the upstream part of the bcr gene. Abl encodes a (non-receptor) protein kinase whereas the function of the bcr gene is unknown. The protein product expresses continuous Abl kinase activity that activates many signal transduction proteins.

An inhibitor of the Abl kinase (imatinib, Gleevec) was discovered in the early 90s. Imatinib binds the active site, blocking the kinase activity, and is very effective at treating CML.

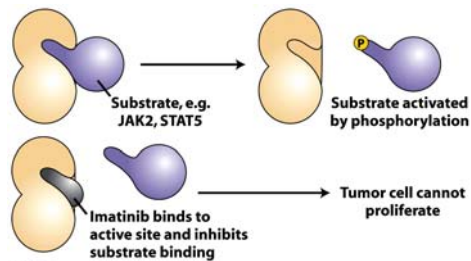


Figure 25-20b
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

BCR-ABL fusion protein

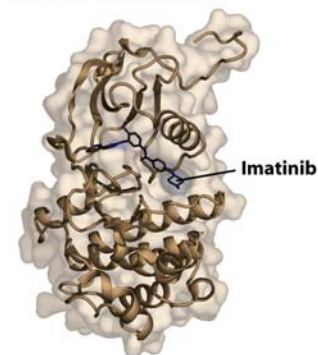
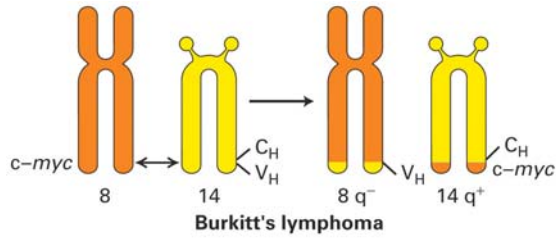


Figure 25-20c
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

Fig. 25-23: Chromosomal translocation in Burkitt's lymphoma.



Translocation of the c-myc gene to a locus controlling transcription of an immunoglobulin gene leads to the overproduction of the Myc transcription factor in lymphocytes and the development of a lymphoma.

Section 25.4: Mutations Causing Loss of Growth-Inhibiting and Cell-Cycle Controls

In normal cells there is an exquisite balance between growth-stimulating and growth-inhibiting signaling pathways.

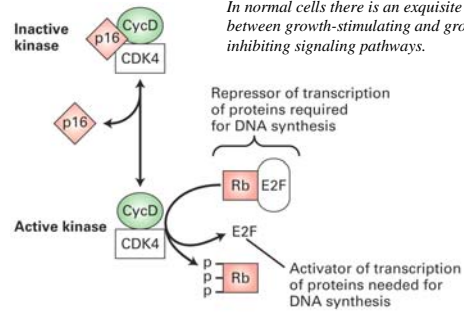


Fig. 25-25: Restriction point control. Overproduction of cyclin D, a positive regulator, or loss of the negative regulators p16 or Rb, commonly occur in human cancers.

Fig. 25-24: Effect of loss of TGF-beta signaling.

TGFβ typically inhibits cell growth. Mutations in the receptor or specific SMADs result in loss of this control and promote cell proliferation.

Smad4 is deleted in some human cancers while in others a mutation in the receptor renders it nonfunctional.

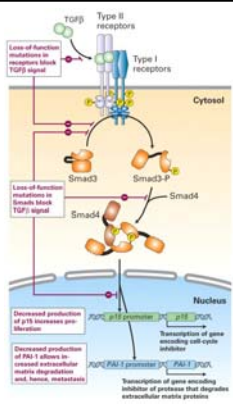
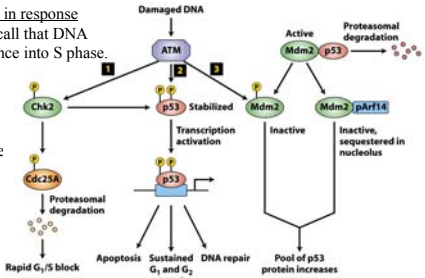


Fig. 25-26: G1 arrest in response to DNA damage. Recall that DNA damage blocks entrance into S phase.

The serine kinase activity of ATM is activated in response to DNA damage. How this occurs is not known. Any hypotheses to test?



Active ATM phosphorylates and activates pathways leading to G1 arrest. Chk2 phosphorylates Cdc25A, leading to its inactivation and inability to activate CDK2. Phosphorylation of p53 stabilizes the protein, allowing it to enhance transcription of a number of genes controlling DNA repair and cell survival. Phosphorylation and inactivation of Mdm2 contributes to the stabilization of p53. P53 is a pro-apoptotic tumor-suppressor gene implicated in many human cancers.

Section 25.5: Carcinogens and Caretaker Genes in Cancer

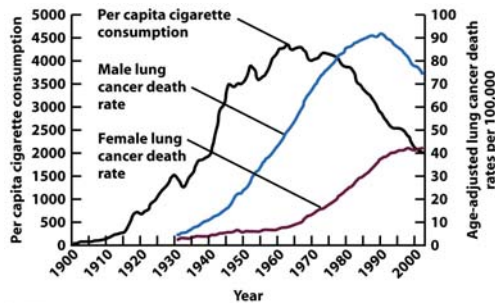


Figure 25-27 Molecular Cell Biology, Sixth Edition © 2008 W. H. Freeman and Company

Fig. 25-31: Loss of telomeres, which occurs normally during DNA replication, limits the number of rounds of cell division.

Telomerase is abundant in stem and germ-line cells but not in somatic cells. The length of the telomere is a measure of replicative capacity.

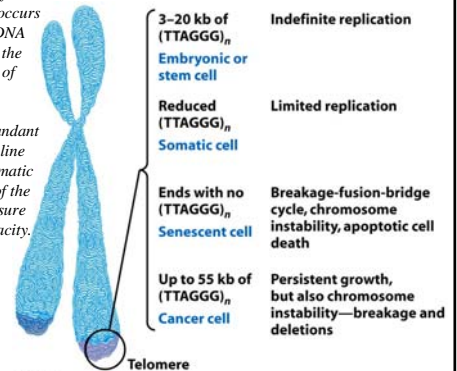


Figure 25-31 Molecular Cell Biology, Sixth Edition © 2008 W. H. Freeman and Company

