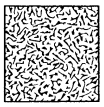


Conclusions

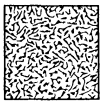
What have we learned about cancer as a molecular disease? First, cancer is the result of mutations in growth control genes—the oncogenes. Cancer is also a multistep process, of which oncogene mutations are only a part. Mutations must also occur in the genes that protect the cell from DNA damage—the tumor suppressor genes. These mutations disrupt the control of cell proliferation that is built into the genome. The mutated cell passes its abnormalities onto its progeny, establishing a clone of itself. The neoplastic cells, because they have damaged tumor suppressor genes, are genetically unstable. The clone evolves into a tumor that acquires the ability to invade tissues and metastasize.

Molecular lesions always precede, usually by quite some time, the clinical appearance of a tumor. Molecular damage is the basis of carcinogenesis. Chemicals that bind to DNA as adducts or radiation that breaks DNA strands, if unrepaired, starts the process. Our understanding of the molecular biology of cancer leads to diagnostic tests that detect these precursor molecular lesions. In a subset of cancers, inherited germline mutations in tumor suppressor genes such as *BRCA*1 are the causes of genetic predisposition to cancer. We are learning how to use genetic screening to advise affected patients. More commonly, cancer arises from acquired somatic mutations. We are beginning to characterize cancers by their specific molecular lesions. Lymphoma and leukemia are defined more precisely by chromosome translocation and oncogene mutations. The evolution of colon cancer can be staged by the progressive molecular lesions that characterize the evolving neoplasia.

The molecular basis of cancer gives us insight into how cancers may be prevented. Squamous cell carcinoma of the cervix provides an example of molecular damage whose cause is known. Infection with certain strains of human papilloma virus inhibits p53 and *RB*1 tumor suppressor gene function. The infected cells are fertile ground for oncogene mutations that cannot be repaired. HPV vaccines under development will likely cure this disease.

The multiple steps in the evolution of cancer also suggest many new targets for molecular anticancer therapies. We can fix mutated oncogenes and tumor suppressor genes by transfection. We can block specific gene malfunctions through antisense or antibodies. We can destroy cancer cells with genetically engineered viruses. Genetic engineering also allows us to manipulate the immune system to turn it against tumors. We can make tissues such as the bone marrow transgenically resistant to anticancer drugs.

At the beginning of this book, I suggested that you look ahead to Table 11.1, a schematic for new anticancer therapies. Now I recommend that you look back a few pages to that same table. Reflect on what we have learned. Armed with this knowledge of the molecular biology of cancer, we can be hopeful. There is so much more that we know and so much more that we can do.



Glossary

***ABL*:** an oncogene that produces a tyrosine kinase; abnormal expression is seen in chronic myeloid leukemia (CML).

allele: one of possible multiple forms of a gene that can occupy the specific chromosomal location for that gene.

aneuploid: abnormal DNA content (see **diploid**).

angiogenesis: the process of inducing blood supply to new tissues; a factor in allowing tumors to grow.

antioncogene: an outdated term used to describe a **tumor suppressor gene.**

antisense oligonucleotide: a short segment of DNA, synthesized to be complementary in genetic sequence to the sense strand of RNA, used to block gene translation.

***APC*:** a tumor suppressor gene, mutated to loss of function in colon cancer.

apoptosis: (Greek, "fallen leaves") the process whereby a cell commits suicide in response to internal signals.

base pair (bp): the smallest unit of information encoded in DNA, referring to one of the rungs on the double helix of DNA.

***bcl*-2:** an oncogene that inhibits normal cell death via **apoptosis.**

***BCR/ABL*:** a gene fusion that occurs with the **Philadelphia chromosomal translocation**; specific marker for chronic myeloid leukemia.

***BRCA*1:** a tumor suppressor gene that when mutated confers a high risk of hereditary breast and ovary cancer.

carcinogenesis: the study of the multiple steps and causes of neoplastic cell growth.

carcinoma *in situ*: a singular stage in the multistep evolution of cancer in which neoplastic cells are present but without invasion.

cell signaling pathway: a process consisting of a series of proteins, encoded by **proto-oncogenes,** that relays extracellular signals into instructions that affect cell growth.

checkpoint: a point in the cell division cycle where the cell is checked for damage to DNA and held back if damage is found.

chemo-protection: chemicals that protect against chemical carcinogens, such as substances that absorb free radicals.

chromosome: a complex structure of DNA and protein carrying part of the genome, visible under the microscope at cellular mitosis where identical pairs are separated into two daughter cells.

chromosomal translocation: an abnormal process where two chromosomes break and exchange pieces.

clonal: a proliferation of genetically identical cells.

codon: three base pairs along DNA code for a single amino acid during the translation of a gene into protein.

***CYCLIN* D1:** a gene on chromosome 11 that produces a protein involved in cell cycle progression, overexpressed when mutated as an oncogene.

diploid: normal DNA content, or 46 chromosomes and 7 picograms, occurring in most cells; see **aneuploid**.

DNA adduct: a chemical complex binding a carcinogen to DNA.

DNA index: a measure of the amount of DNA in cells, with normal diploid DNA content as a reference index of 1.0—also called ploidy index.

DNA polymerase: an enzyme that enables synthesis of DNA from a DNA template strand.

DNA vaccines: a new class of vaccines based on DNA inserting into the cell; the intracellular translation of this DNA produces MHC type I immunity; a possible vaccination method for HPV and HIV.

dominant: a gene that when present as only one copy out of two alleles produces sufficient functional protein to have an effect; the opposite of **recessive**.

exon: a segment of DNA within a gene that codes for protein, separated from adjacent exons by noncoding segments called **introns**.

familial adenomatous polyposis coli (FAP): a syndrome due to the inherited loss of the ***APC*** tumor suppressor gene that results in the development of numerous colon polyps with a high probability of cancer if untreated.

FISH: fluorescent *in situ* hybridization, a method for analysis of chromosomes and DNA by use of fluorescent DNA probes and microscopy.

flow cytometry: the quantitative measure of cellular parameters such as DNA content by laser light scattering technology.

frame shift: a type of mutation in which the reading of triplet **codon** DNA sequences is shifted out of phase producing a **nonsense** message.

G protein: a group of intracytoplasmic proteins coded for by oncogenes; part of the **cell signal pathway**.

G0: a nonproliferating phase of the cell cycle consisting of a reservoir of cells that have completed mitosis but have halted further division.

G1: a phase of the cell division cycle occurring after mitosis (**M**) and before DNA synthesis (**S**).

G2: a phase of the cell division cycle occurring after DNA synthesis (**S**) and before mitosis (**M**).

gene: a segment of DNA that encodes a message, usually the amino acid sequence of a protein as well as information controlling the expression of this information.

genotype: a specific informational set carried as a gene or group of genes, but not necessarily expressed.

germline: the genome of an organism at birth, before any mutations or rearrangements.

graft versus host disease (GVHD): a reaction by transplanted (donor) immune cells against cells of the host.

haploid: half normal DNA content (one half of 46 **chromosomes**) occurring in germ cells; see **diploid**.

***her-2/neu*:** an oncogene coding for a cell surface receptor; overexpressed in 25% to 35% of breast cancers.

hereditary nonpolyposis colon cancer (HNPCC): a syndrome caused by inherited loss of mismatched repair genes.

HPV: human papilloma virus, a factor in viral **carcinogenesis** of squamous cell carcinoma of the cervix.

HSV-tk: a **kit** for transfecting a thymidine kinase gene into a cell using herpes simplex virus as a vector.

HTLV-1: a retrovirus with transforming ability related to adult T-cell lymphoid leukemia.

hybridization: the binding of probe to target, used for DNA and protein molecular studies.

IgH: a symbol for the immunoglobulin heavy chain gene.

image cytometry: the quantitative measure of cellular parameters by computer assisted microscopy.

initiator: a chemical carcinogen that is part of the process of inducing mutations that cause neoplastic proliferation.

intron: a segment of DNA within a gene that does not code for a protein, occurring as a space between **exons**.

in vitro: (Latin, "in glass") a process studied outside the body, usually in a cell culture.

karyotype: an analysis of the chromosome content of cells by microscopic examination. A normal human karyotype is 46XY or 46XX.

kit: a commercially available packaged process consisting of the methods and materials necessary to carry out a fundament step in biotechnology.

loss of heterozygosity (LOH): a genetic mechanism that results in damage to the second allele of a gene by incorrect copying or conversion from the first mutated allele.

M: mitosis, a phase of the cell division cycle, recognizable by the appearance of **chromosomes**.

MDR: multi-drug resistance gene; produces a 170-kd glycoprotein that pumps toxic substances out of a cell; amplification of this gene is a mechanism for drug resistance in tumors.

microsatellite instability: a genetic phenomenon in which short repeating DNA sequences undergo multiple and varying repeats when copied; leads to further mutations.

mismatch repair genes: a group of DNA repair genes, also classified as tumor suppressor genes that when mutated lead to **microsatellite instability** and further mutation, a cause of **HNPCC** syndrome.

mutation: a change in DNA that produces a change in phenotype, usually away from what is considered to be normal (see **polymorphism**).

***myc*:** a family of oncogenes that produce a DNA transcription factor that stimulates cell division.

neoplastic: a cellular proliferation not under normal controls; may be clinically benign or malignant.

neural network: a computational method that allows for comparison of multiple parameters affecting a process.

nonsense: a DNA segment that does not code for amino acids having no open reading frame.

Northern blot: a method of analyzing RNA.

oncogene: the mutated form of a growth control gene; a step in the formation of a tumor.

open reading frame, ORF: a long segment of DNA that when read as

triplets, produces a set of codons that does not include a STOP codon; an ORF is a sign that this segment of DNA is part of a gene.

p53: a **tumor suppressor gene** mutated in many cancers resulting in loss of a **checkpoint** for DNA damage.

PCR: polymerase chain reaction, a method for amplifying pieces of DNA; used as a detection method and to produce pieces for further study; a mainstay of recombinant DNA technology.

pharming: the process of creating new molecules by growing them in genetically altered plants or animals.

Philadelphia chromosome: a **t(9;22) chromosomal translocation** that is a marker for the neoplastic clone in chronic myeloid leukemia.

phenotype: the physical expression of a specific gene or group of genes; see **genotype**.

polymorphism: a change in DNA that produces no change in phenotype.

promoter: a substance that stimulates cell growth such that when combined with a chemical **initiator** leads to neoplastic cell growth, part of **carcinogenesis**.

proto-oncogene: the normal cellular form of a gene that controls cell growth, that when mutated becomes an **oncogene**.

recessive: a gene that only when present as both copies of two possible alleles results in a characteristic phenotype; the opposite of **dominant.**

replicon: a structure on the DNA strand that carries out the functions of copying during DNA synthesis.

restriction enzyme: an enzyme, derived from bacteria that cuts DNA at a specific site based on nucleotide sequence; a major tool of recombinant DNA technology.

retrovirus: an RNA virus that uses the cell's own genes to help it replicate; posesses the unique enzyme **reverse transcriptase**.

reverse transcriptase: an enzyme that copies RNA into DNA, reversing the normal flow of genetic information.

S: a phase of the cell division cycle in which DNA synthesis occurs.

S phase fraction: the percent of cells in a tissue that are currently synthesizing DNA; a measure by **cytometry** of the cell proliferation.

somatic (line): refers to the genome of tissues that may be altered from the **germline** by mutation or rearrangement.

Southern blot: a method for analyzing DNA by electrophoresis and hybridization blotting, named after Ed Southern.

splice acceptor site: a DNA sequence where DNA is cut and rearranged; these sites seem predisposed to erroneous rejoining and **chromosomal translocation**.

***src*:** a **viral oncogene** with **transforming** ability seen in the Rous sarcoma retrovirus.

t(9;22): karyotype nomenclature for the **Philadelphia chromosome** and ***BCR/ABL*** gene fusion seen in chronic myeloid leukemia.

Taq: a special **DNA polymerase** that is stable at high temperatures; used in PCR; pronounced "tack."

telomerase: a DNA polymerase that replicates **telomeres**; may be abnormal in tumor cells allowing unlimited numbers of cell division.

telomere: a genetic element at the end of a chromosome consisting of a repetitive DNA sequence that becomes progressively shorter with each cell division.

tetraploid: twice normal DNA content, or 92 chromosomes occurring in dividing cells just before mitosis, also occurring abnormally in some tumors.

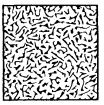
transform: a genetic mutation that results in continuous cell growth **in vitro**.

transgenic: an organism whose heredity has been altered by biotechnology.

viral oncogene: the viral form of a cell growth control gene or **proto-oncogene**, seen in some **retroviruses.**

Western blot: a method for analyzing proteins.

185delAG: a specific deletion in the ***BRCA*1** breast cancer susceptibility gene; refers to a deletion of nucleotides A and G at position 185 in the gene.



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