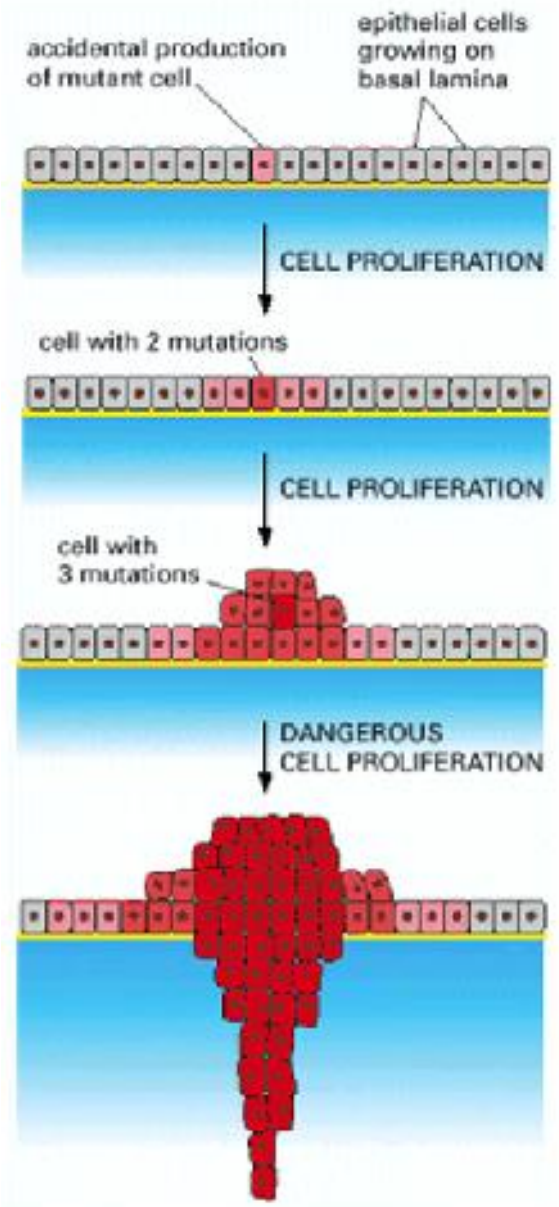
Cancer

-Dr. Ekta Khare

Cancer

- Many proteins involved in DNA repair, cell signaling, the cell cycle and programmed cell death, and tissue architecture were discovered because abnormalities in their function can lead to the uncontrolled proliferation, genetic mayhem, and other antisocial behavior characteristic of cancer cells.
- Thus, unlike free-living cells such as bacteria, which compete to survive, the cells of a multicellular organism are committed to collaboration. To coordinate their behavior, the cells send, receive, and interpret an elaborate set of signals that serve as social controls, telling each of them how to act.
- As a result, each cell behaves in socially responsible manner, resting, dividing, differentiating, or dying as needed for the good of the organism. Molecular disturbances that upset this harmony mean trouble for a multicellular society.
- In a human body with more than 1014 cells, billions of cells experience mutations every day, potentially disrupting the social controls.
- Most dangerously, a mutation may give one cell a selective advantage, allowing it to divide more vigorously than its neighbors and to become a founder of a growing mutant clone.
- A mutation that gives rise to such selfish behavior by individual members of the cooperative can jeopardize the future of the whole enterprise. Repeated rounds of mutation, competition, and natural selection operating within the population of somatic cells cause matters to go from bad to worse.
- These are the basic ingredients of cancer: it is a disease in which individual mutant clones of cells begin by prospering at the expense of their neighbors, but in the end destroy the whole cellular system.

Figure 23-11. Clonal evolution. A tumor develops through repeated rounds of mutation and proliferation, giving rise eventually to a clone of fully malignant cancer cells. At each step, a single cell undergoes a mutation that enhances cell proliferation, so that its progeny become the dominant clone in the tumor. Proliferation of this clone then hastens occurrence of the next step of tumor progression by increasing the size of the cell population at risk of undergoing an additional mutation.



Cancer Cells Reproduce Without Restraint and Colonize Foreign Tissues

- Cancer cells are defined by two heritable properties: they and their progeny (1) reproduce in defiance of the normal restraints on cell division and (2) invade and colonize territories normally reserved for other cells.
- It is the combination of these actions that makes cancers peculiarly dangerous.
- An isolated abnormal cell that does not proliferate more than its normal neighbors does no significant damage, no matter what other disagreeable properties it may have; but if its proliferation is out of control, it will give rise to a tumor, or neoplasm a relentlessly growing mass of abnormal cells.
- As long as the neoplastic cells remain clustered together in a single mass, however, the tumor is said to be benign.
- At this stage, a complete cure can usually be achieved by removing the mass surgically. A tumor is considered a cancer only if it is malignant, that is, only if its cells have acquired the ability to invade surrounding tissue.
- Invasiveness usually implies an ability to break loose, enter the bloodstream or lymphatic vessels, and form secondary tumors, called metastases, at other sites in the body.
- The more widely a cancer spreads, the harder it becomes to eradicate.
- Cancers are classified according to the tissue and cell type from which they arise.
- Cancers arising from epithelial cells are termed carcinomas; those arising from connective tissue or muscle cells are termed sarcomas.
- Cancers that do not fit in either of these two broad categories include the various leukemias, derived from hemopoietic cells, and cancers derived from cells of the nervous system.

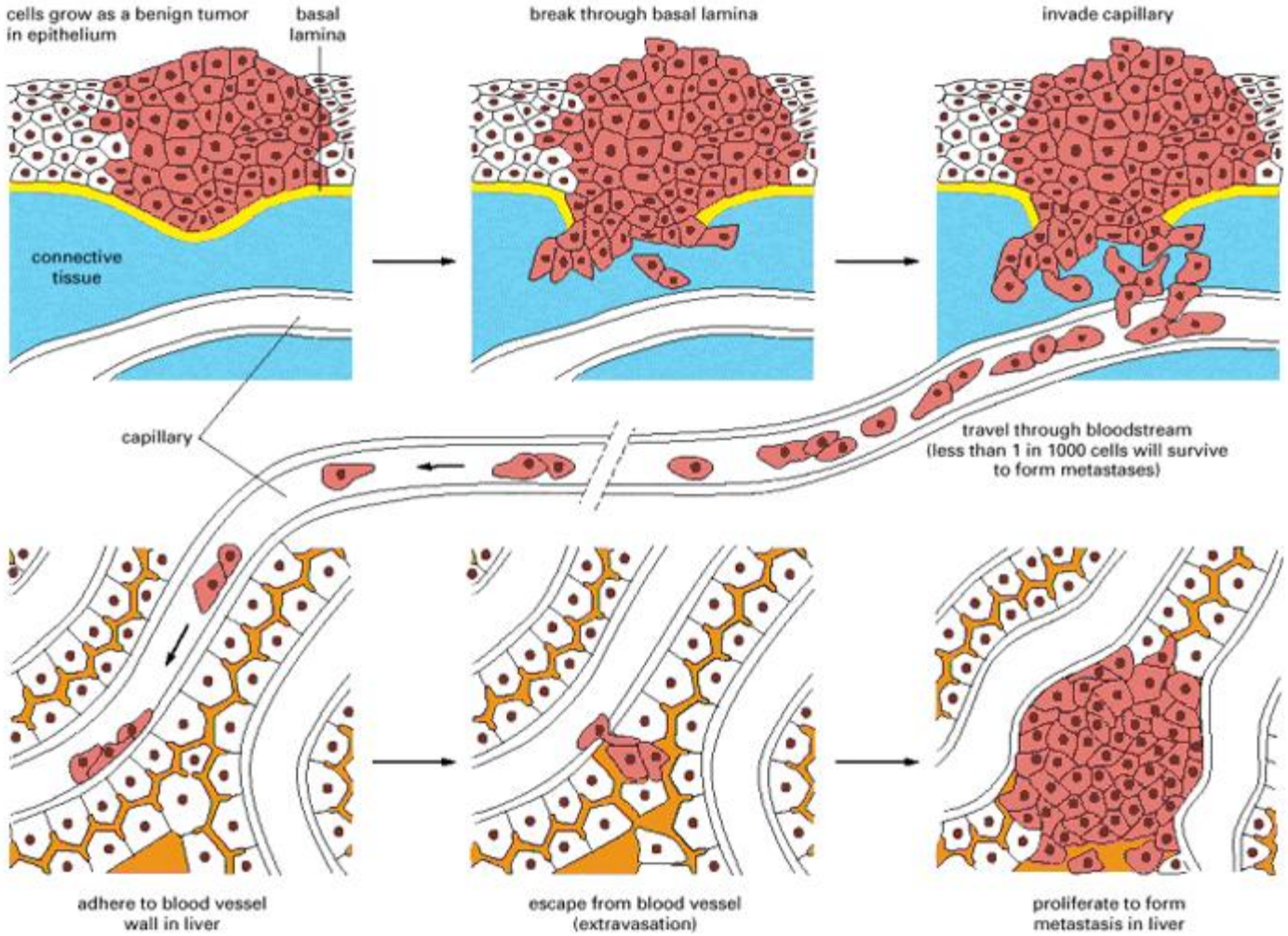


Figure 23-15. Steps in the process of metastasis. This example illustrates the spread of a tumor from an organ such as the lung or bladder to the liver. Tumor cells may enter the bloodstream directly by crossing the wall of a blood vessel, as diagrammed here, or, more commonly perhaps, by crossing the wall of a lymphatic vessel that ultimately discharges its contents (lymph) into the bloodstream. Tumor cells that have entered a lymphatic vessel often become trapped in lymph nodes along the way, giving rise to lymph-node metastases. Studies in animals show that typically far less than one in every thousand malignant tumor cells that enter the bloodstream will survive to produce a tumor at a new site.

- About 90% of human cancers are carcinomas, perhaps because most of the cell proliferation in the body occurs in epithelia, or because epithelial tissues are most frequently exposed to the various forms of physical and chemical damage that favor the development of cancer.
- One clear demonstration of clonal evolution comes from analysis of the chromosomes in tumor cells.
- Chromosomal aberrations and rearrangements are present in the cells of most common cancers.
- For those cancers that have a discernible external cause, the disease does not usually become apparent until long after exposure to the causal agent: the incidence of lung cancer does not begin to rise steeply until after 10 or 20 years of heavy smoking.
- The rate of tumor evolution and progression is accelerated both by mutagenic agents (tumor initiators) and by nonmutagenic agents (tumor promoters) that affect gene expression, stimulate cell proliferation, and alter the ecological balance of mutant and nonmutant cells.
- The majority of known cancer-causing agents are mutagens, including chemical carcinogens, certain viruses, and various forms of radiation such as UV light and ionizing radiation.
- Because many factors contribute to the development of a given cancer some of which are under our control a large proportion of cancers are in principle preventable.

Viruses and Other Infections Contribute to a Significant Proportion of Human Cancers

- A small but significant proportion of human cancers, perhaps 15% in the world as a whole, are thought to arise by mechanisms that do involve viruses, bacteria or parasites.
- The main culprits are the DNA viruses.
- Evidence for their involvement comes partly from the detection of viruses in cancer patients and partly from epidemiology.
- Liver cancer, for example, is common in parts of the world (Africa and Southeast Asia) where hepatitis-B viral infections are common, and in those regions the cancer occurs almost exclusively in people who show signs of chronic hepatitis-B infection.
- Viruses can either alter a cell's DNA directly or act as tumor promoters.
- DNA viruses frequently carry genes that can subvert the control of cell division in the host cell, causing uncontrolled proliferation.
- DNA viruses that operate in this manner include the human papillomaviruses; some of these viruses cause warts, while others infect the uterine cervix and are implicated in the development of carcinomas of the cervix.

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- To make many infectious virus particles from a single host cell, a DNA virus has to commandeer this machinery and drive it hard, breaking through the normal constraints on DNA replication and usually killing the host cell in the process.
- Typically, however, the virus also has another option: it can propagate its genome as a quiet, well-behaved passenger in the host cell, replicating in parallel with the host cell's DNA in the course of ordinary cell division cycles.
- The virus can switch between these two modes of existence.
- Genetic accidents can occur, such that the virus misuses its equipment for commandeering the DNA replication machinery, and instead of switching on rapid replication of its own genome, switches on persistent proliferation of the host cell.

DNA Viruses

- DNA viruses such as papillomaviruses can promote the development of cancer by sequestering the products of tumor suppressor genes in particular, the Rb protein, which regulates cell division, and the p53 protein, which is thought to act as an emergency brake on cell division in cells that have suffered genetic damage and to call a halt to cell division in senescent cells with shortened telomeres.
- The p53 protein has a dual role, regulating both progression through the cell cycle and the initiation of apoptosis.
- So loss or inactivation of p53, which occurs in about half of all human cancers, is doubly dangerous: it allows genetically damaged and senescent cells to continue to replicate their DNA, increasing the damage, and it allows them to escape apoptosis.
- The loss of p53 function may contribute to the genetic instability of many full-blown metastasizing cancers.
- In papillomaviruses, the viral genes that are mainly to blame are called E6 and E7. The products of these viral oncogenes interact with many host cell proteins, but in particular they bind to the protein products of two key tumor suppressor genes of the host cell, putting them out of action and so permitting the cell to replicate its DNA and divide in an uncontrolled way.
- One of these host proteins is Rb: by binding to Rb, the viral E7 protein prevents it from binding to its normal associates in the cell. The other host protein inactivated by the virus is the tumor suppressor p53, which is bound by the viral E6 protein, triggering p53 destruction.

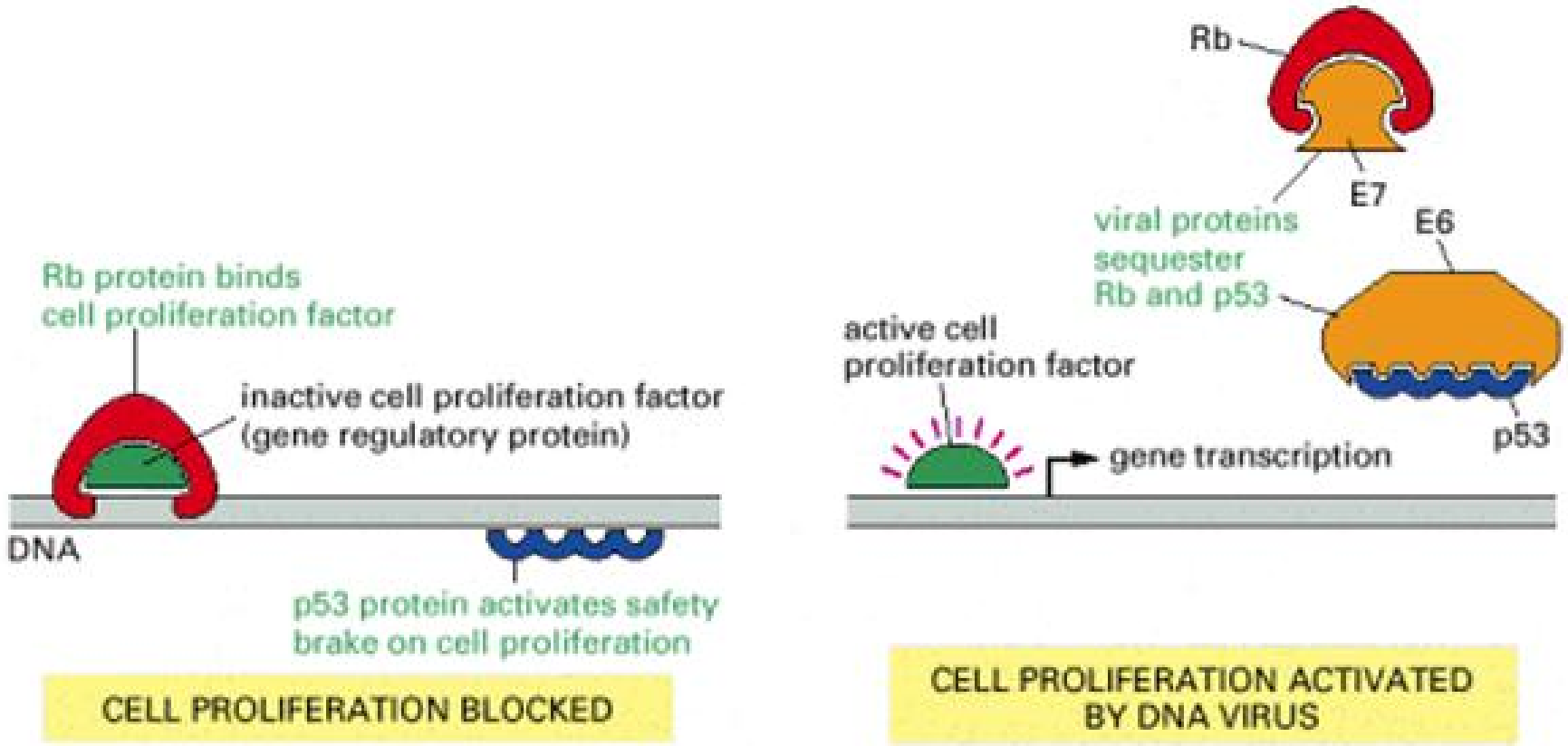

Figure 23-35. Activation of cell proliferation by a DNA tumor virus.
Papillomavirus uses two viral proteins, E6 and E7, to sequester the host cell's p53 and Rb respectively. The SV40 virus (a related virus that infects monkeys) uses a single dual-purpose protein called large T antigen, for the same purpose. The E6 protein binding leads to ubiquitylation of its p53 partner, inducing p53 proteolysis (not shown).

VIRUS	ASSOCIATED TUMORS	AREAS OF HIGH INCIDENCE
DNA Viruses		
Papovavirus family		
Papillomavirus	warts (benign)	worldwide
(many distinct strains)	carcinoma of the uterine cervix	worldwide
Hepadnavirus family		
Hepatitis-B virus	liver cancer (hepatocellular carcinoma)	Southeast Asia, tropical Africa
Herpesvirus family		
Epstein-Barr virus	Burkitt's lymphoma (cancer of B lymphocytes)	West Africa, Papua New Guinea
	nasopharyngeal carcinoma	southern China, Greenland
RNA viruses		
Retrovirus family		
Human T-cell leukemia virus type I (HTLV-1)	adult T-cell leukemia/ lymphoma	Japan, West Indies
Human immuno-deficiency virus (HIV, the AIDS virus)	Kaposi's sarcoma	Central and Southern Africa

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- In some other cancers, viruses seem to have additional, indirect tumor promoting actions; the hepatitis-B virus may, for example, favor the development of liver cancer by doing damage that provokes cell division in the liver, as well as by altering cell growth control directly.
- In AIDS, the human immunodeficiency virus (HIV) promotes development of an otherwise rare cancer called Kaposi's sarcoma by destroying the immune system, thereby permitting a secondary infection with a human herpes virus (HHV-8) that has a direct carcinogenic action.
- Chronic infection with parasites and bacteria may also promote the development of some cancers.
- For example, infection of the stomach with the bacterium *Helicobacter pylori*, which causes ulcers, appears to be a major cause of stomach cancer.
- And bladder cancer in some parts of the world is associated with infection by the blood fluke, *Schistosoma.*

Cancer: at a molecular level

- Cancer-critical genes are grouped into two broad classes, according to whether the cancer risk arises from too much activity of the gene product, or too little.
- Genes of the first class, for which a gain-of-function mutation drives a cell toward cancer, are called **proto-oncogenes**; their mutant, overactive forms are called oncogenes.
- Genes of the second class, for which a loss-of-function mutation creates the danger, are called **tumor suppressor genes**.

Oncogenes

- DNA from human tumors, led to the first direct identification of an oncogenic mutation in a human cancer.
- Several overactive growth-promoting genes were identified by isolating and sequencing the DNA fragments that had been transferred to these transformed cells.
- The first of these genes to be sequenced was a mutant version of the *Ras* gene, which is now known to be mutated in about one in four human tumors.
- Retroviruses, we now know, are capable of picking up, at random, fragments of genetic material from their animal hosts and ferrying them from one infected individual to another.
- Occasionally, a proto-oncogene is picked up, in a damaged or misregulated form that turns it into an oncogene.
- Infection with a virus that carries such a cargo can trigger tumors in some animal species, and a large number of oncogenes were first discovered in this way.

…Oncogenes

- Normal Ras proteins are monomeric GTPases that help to transmit signals from growth factor receptors on the cell surface.
- The point mutations found in Ras genes isolated from human tumors generate a hyperactive Ras protein that persists abnormally in its active state transmitting an inappropriate signal for cell proliferation.
- Because this type of mutation makes a gene product hyperactive, the effect is dominant only one of the cell's two gene copies needs to undergo the change.
- The Ras genes are mutated in a wide range of human cancers, and they remain one of the most important examples of cancer-critical genes.

Tumor Suppressor Genes

- The key insight that led to the discovery of the first tumor suppressor gene came from studies of a rare type of human cancer, retinoblastoma, which arises from cells in the body that are converted to a cancerous state by an unusually small number of mutations.
- There are two forms of the disease, one hereditary, the other not.
- Some individuals with hereditary retinoblastoma have a visibly abnormal karyotype, with a deletion of a specific band on chromosome 13.
- Deletions of this same locus are also encountered in tumor cells from some patients with the nonhereditary disease, suggesting that the cancer may be caused by loss of a critical gene in that chromosomal region.
- The hereditary form of the disease, a deletion or loss-of-function mutation occurs in one copy of the **Rb gene** in every cell of the body.
- Thus, these cells are predisposed to becoming cancerous, but are not actually cancerous so long as they retain one good copy of the gene.
- The retinal cells that do become cancerous are defective in both copies of Rb because a somatic mutation has occurred, in addition to the original inherited mutation, and has eliminated the remaining good copy.
- Nonhereditary retinoblastomas are very rare, because they require the coincidence of two somatic mutations in a single retinal cell lineage, so as to destroy both copies of the Rb gene.
- The Rb gene encodes the Rb protein, which is a universal regulator of the cell cycle that is normally expressed in almost all the cells of the body.
- Because it acts as one of the main brakes on progress through the cell-division cycle, the loss of Rb can allow cells to enter the cell division cycle inappropriately.

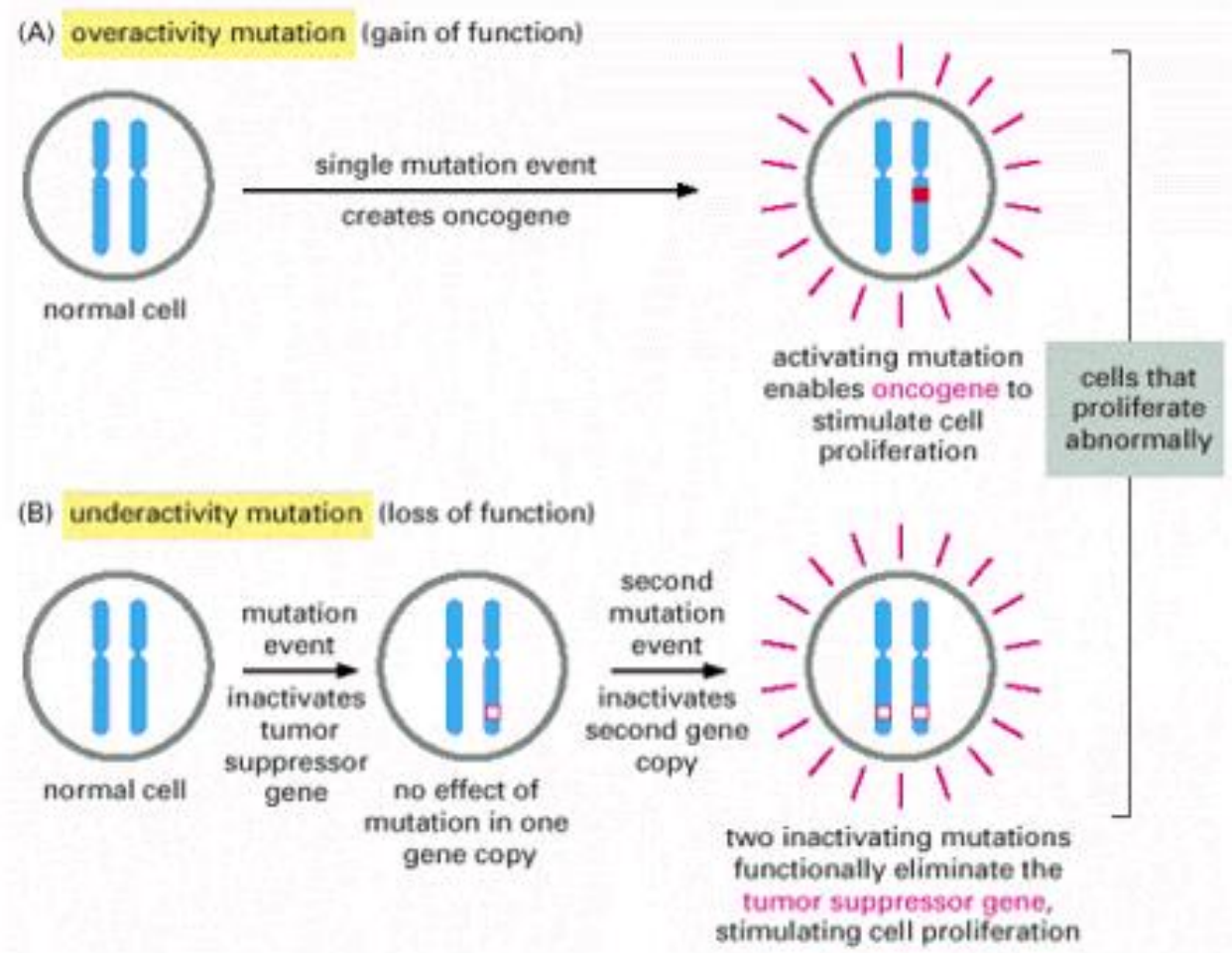

Figure 23-24. Cancer-critical genes fall into two readily distinguishable categories, dominant and recessive. Oncogenes act in a dominant manner: a gain-of-function mutation in a single copy of the cancer-critical gene can drive a cell toward cancer. Tumor suppressor genes, on the other hand, generally act in a recessive manner: the function of both alleles of the cancer-critical gene must be lost to drive a cell toward cancer. In this diagram, activating mutations are represented by solid red boxes, inactivating mutations by hollow red boxes.

Gene mutations

- The types of genetic alterations that can make a cancer-critical gene into an oncogene fall into three basic categories.
- The gene may be altered by a small change in sequence such as a **point mutation**, by a larger-scale change such as a **partial deletion**, or by a **chromosomal translocation** that involves the breakage and rejoining of the DNA helix.
- These changes can occur in the protein-coding region so as to yield a hyperactive product, or they can occur in adjacent control regions so that the gene is simply expressed at concentrations that are much higher than normal.
- Alternatively, the cancer-critical gene may be overexpressed because extra copies are present due to **gene amplification** events caused by errors in DNA replication.
- Members of **the Myc proto-oncogene** family, on the other hand, are not usually activated by mutations in the protein coding region; instead the genes are overexpressed or amplified.
- In normal cells, the Myc protein acts in the nucleus as a signal for cell proliferation.
- Although Myc is frequently amplified in cancers, it can also be made active by a chromosomal translocation.
- As a result of this rearrangement, powerful gene regulatory sequences are placed inappropriately next to the Myc protein coding sequence, producing unusually large amounts of Myc mRNA.
- For example, in Burkitt's lymphoma a translocation brings the Myc gene under the control of sequences that normally drive the expression of antibodies in B cells. As a result, the mutant B cells proliferate to excess and form a tumor.

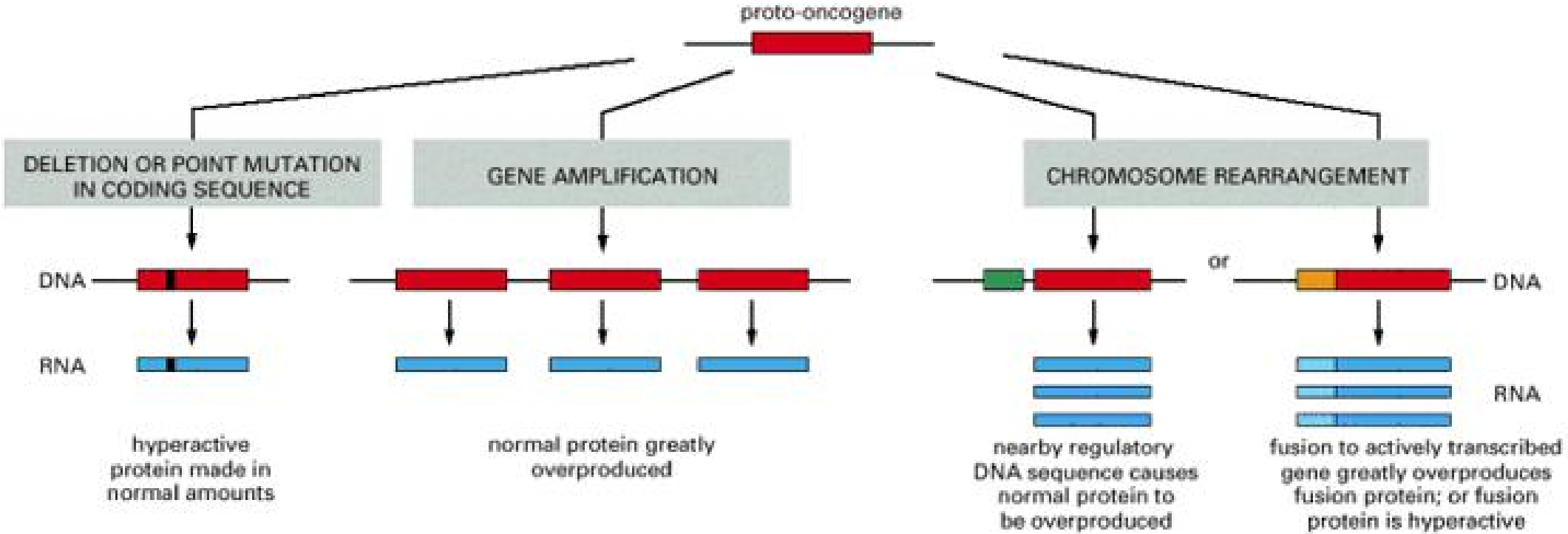

Figure 23-27. Three ways in which a proto-oncogene can be made overactive to convert it into an oncogene.