Az ionizáló sugárzás karcinogén hatása

I. A spontán daganat kialakuláshoz vezető sejtszintű károsodások
II. Ionizáló sugárzás által okozott sejtszintű elváltozások
    1. DNS sérülések
    2. DNS károsodás kijavítása
    3. Ionizáló sugárzás hatása a sejtciklusra
    4. Közvetlen sugárhatásra kialakuló mutációk típusai
III. Ionizáló sugárzás hatására kialakuló daganatokban megjelenő onkogén elváltozások
IV. Genetikai instabilitás szerepe a sugárzás gerjesztette daganat kialakulásban
V. A szervezet védekező mechanizmusai
VI. A lineáris, küszöbdózis nélküli daganat kialakulás molekuláris biológiai kritikája

Spontán daganatok kialakulásának mechanizmusa

A daganatkeletkezés lépései

(immortalizácó)

(⇄) Iniciáció → promoció → progresszió → kontrollálatlan proliferáció → daganat

Inzultus

spontán ionizáló sugárzás UV, virus kémiai ágens	növekedési faktorok sugárzás ? hormonok kemikáliák	sejtproliferáció serkentése, pl. sugárzás okozta sejtdepléció.

Mechanizmus

Onkogén aktiváció mutáció, inszerció, amplifikáció következtében; virusok; kromoszóma átrende-ződés, tumor szuppresszor gének sérülése mutáció, deléció és transzlokáció miatt	genetikai instabilitás	a hibák progresszív növekedése, metasztatizáló hajlam megjelenése

Küszöbdózis

valószínűleg nincs	valószínűleg van

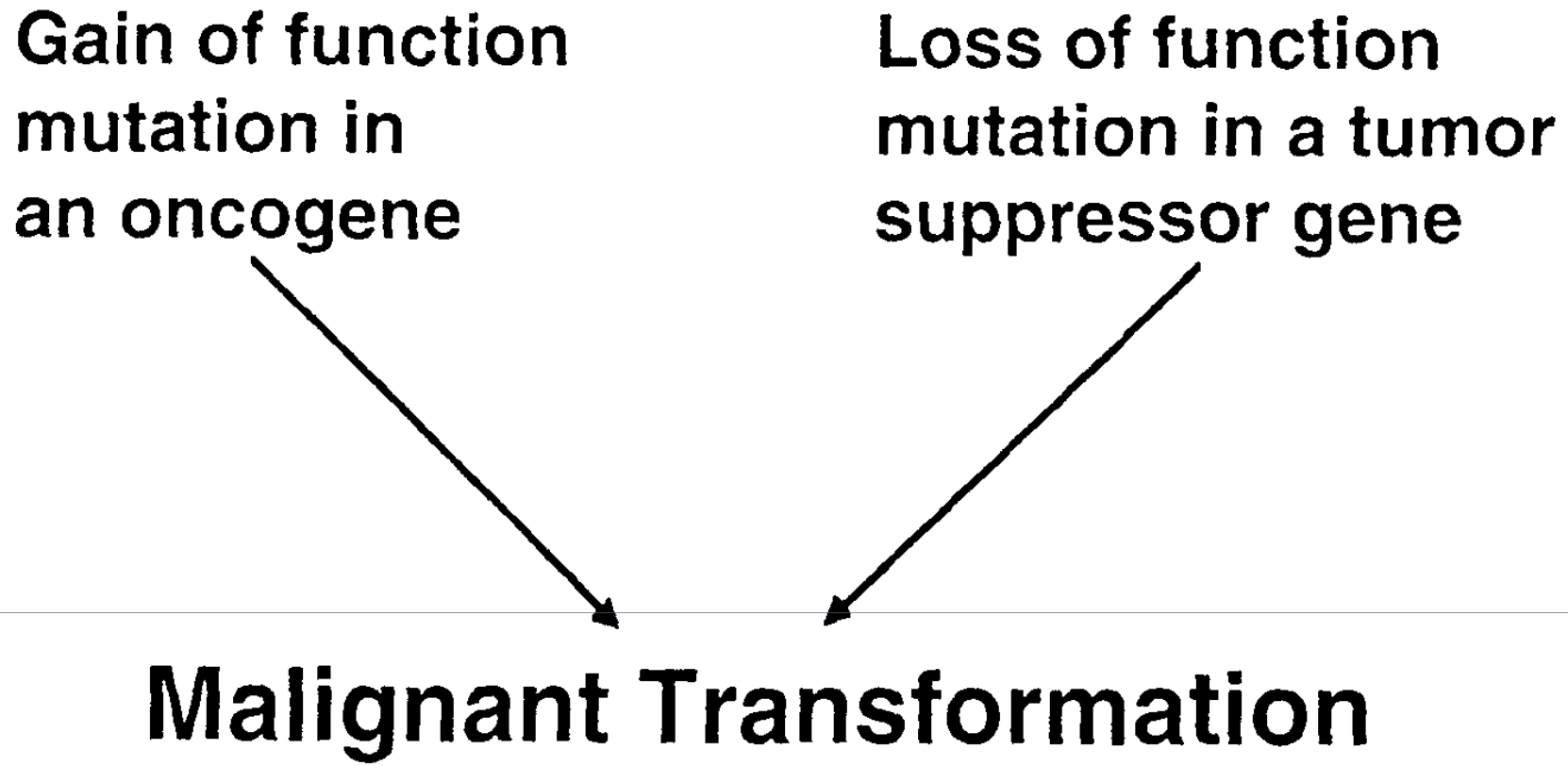


Figure 17.1. The process of malignant transformation may result from either a gain-of-function mutation that activates an oncogene, or a loss-of-function mutation in a tumor-suppressor gene.

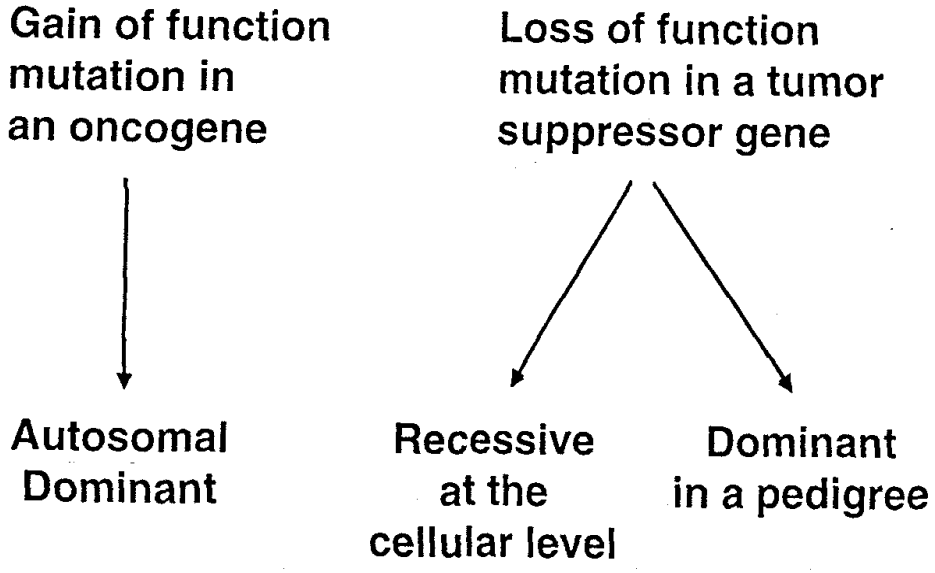


Figure 17.7. Gain-of-function mutations that result in the activation of an oncogene require only one copy to be activated; that is, oncogenes act in a dominant fashion. Loss-of-function mutations that inactivate a tumor-suppressor gene require both copies to be inactivated for the malignant phenotype to be expressed; that is, tumor-suppressor genes act in a recessive fashion. This may be true at a cellular level; however, in viewing the pedigree of a cancer-prone family, the loss of a tumor-suppressor gene may appear to be inherited as a dominant mutation.

Onkogének aktivációja

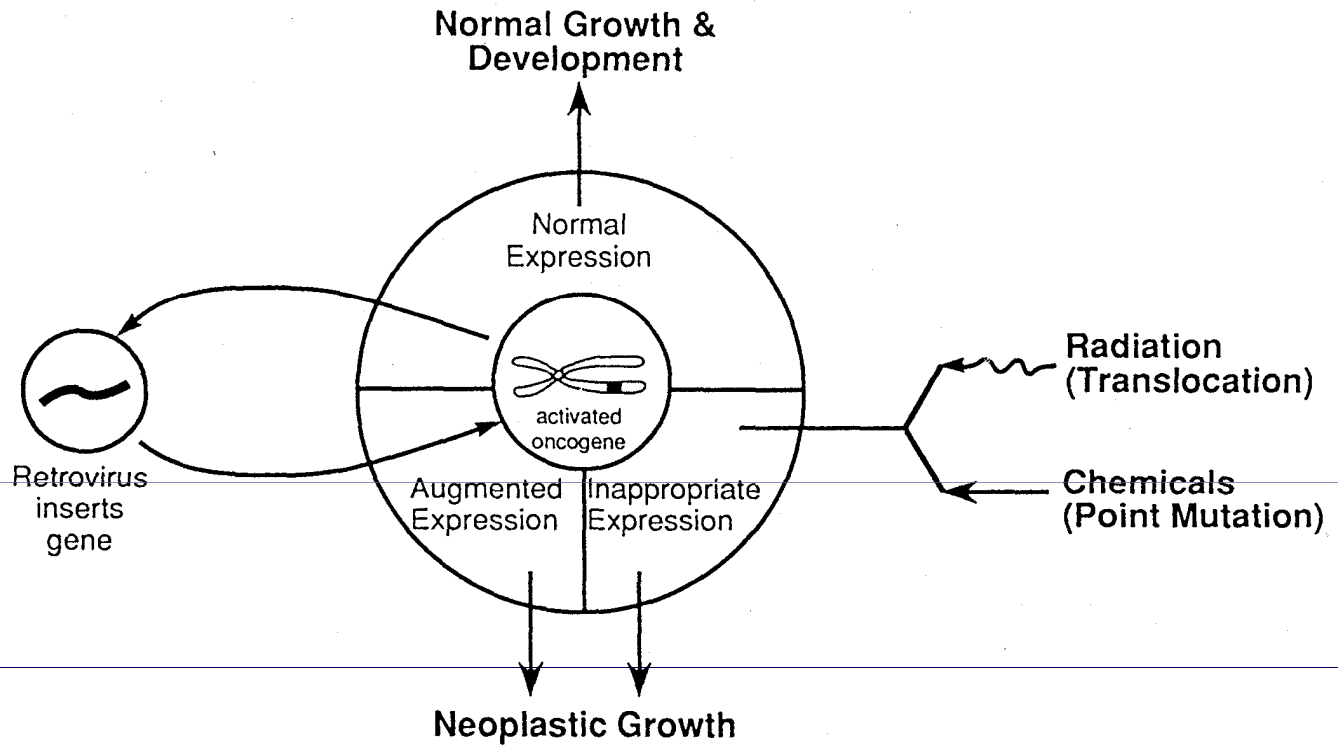


Figure 17.2. The way in which the concept of oncogenes provides a ready answer for how agents as diverse as viruses, radiations, and chemicals all can induce tumors that are essentially indistinguishable from another. The retrovirus inserts a gene; a chemical may activate an endogenous oncogene by a point mutation; radiation may do the same by, for example a translocation. (Adapted from Bishop JM: Cellular oncogene retroviruses. Ann Rev Biochem 52:301–354, 1983, with permission.)

TABLE 17.1. *Chromosomal Changes Leading To Oncogene Activation and the Human Malignancies Associated With Them*

Oncogene	Chromosomal Changes	Human Cancers
N-*ras*	Deletion (1)	Neuroblastoma
Blym	Deletion (1)	Neuroblastoma
fms	Deletion (5)	Acute nonlymphocytic leukemia
H-*ras*	Deletion (11)	Sarcoma
c-*abl*	Translocation (9–12)	Chronic myelogenous leukemia
c-*myc*	Translocation (8–14)	B-cell lymphoma
	Translocation (2–8)	Burkitt's lymphoma
N-*myc*	Translocation (2–8)	Burkitt's lymphoma
raf	Translocation (3–8)	Parotid gland tumor
myb	Translocation (6–14)	Carcinoma
mas	Translocation (3–8)	Acute myelocytic leukemia
abl	Translocation (9–22)	Chronic myelogenous leukemia
sis	Translocation (9–22)	Chronic myelogenous leukemia
	Translocation (8–22)	Burkitt's lymphoma
N-*myc*	Gene amplification	Neuroblastoma
neu	Gene amplification	Breast carcinoma

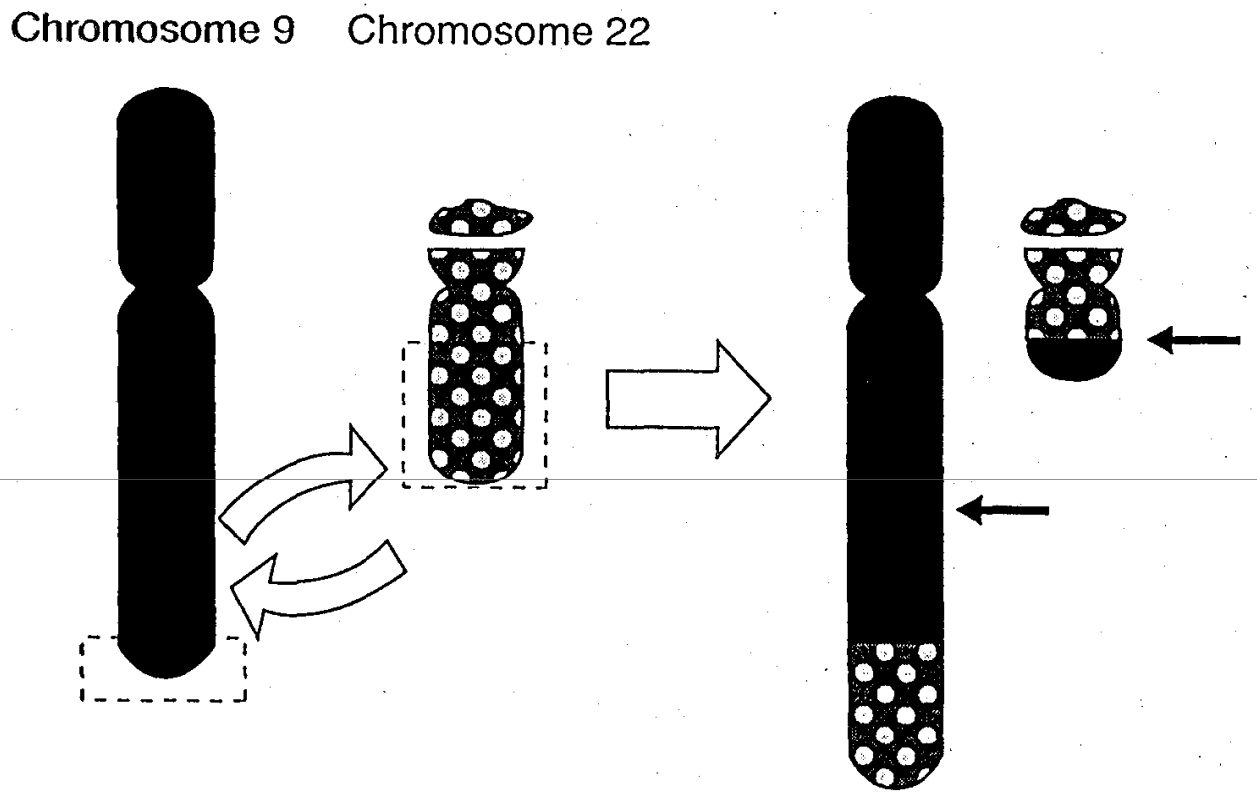


Figure 17.3. How a symmetric translocation between chromosomes 9 and 22 brings together the *bcl-2* and *abl* genes to form a fusion gene, associated with over 90% of cases of chronic myelogenous leukemia (CML).

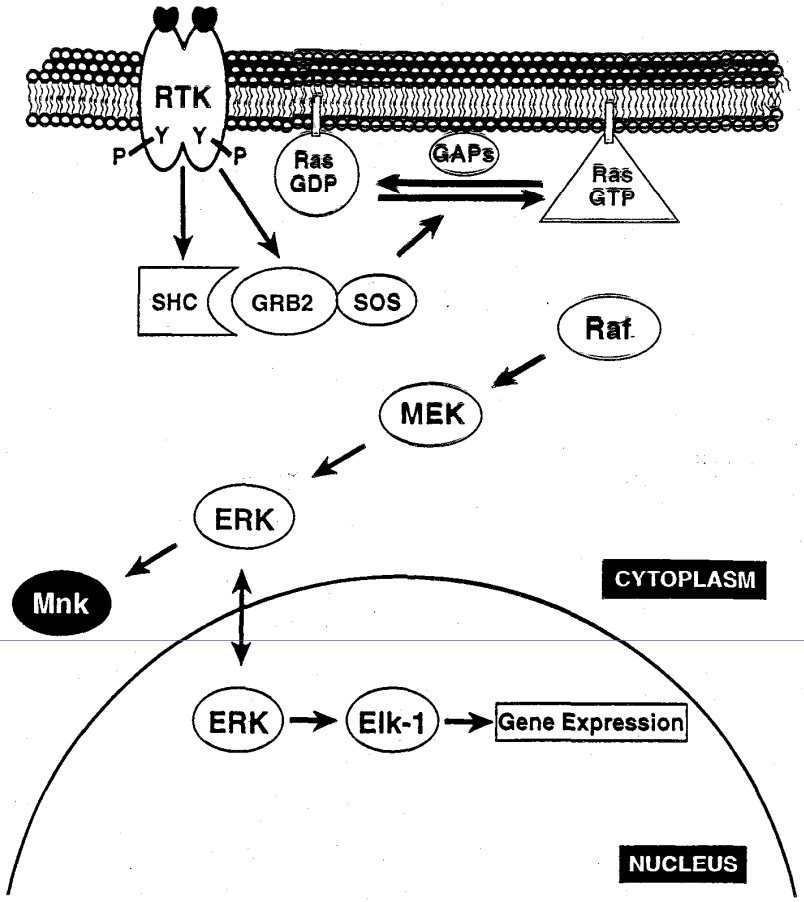


Figure 17.11. *Ras* mediates its effect on cellular proliferation, at least in part, by the activation of a cascade of kinases. *Ras* is a GDP/GTP-regulated binary switch that resides at the inner surface of the plasma membrane and acts to relay extracellular ligand-stimulated signals to cytoplasmic signaling cascades. A linear pathway in which *ras* functions downstream of receptor tyrosine kinases and upstream of a cascade of serine–threonine kinases provides a complete link between the cell surface and the nucleus. Activated ERKs can translocate into the nucleus to phosphorylate and activate transcription factors, such as Elk-1. Activated ERKs also phosphorylate substrates in the cytoplasm, including the Mnk kinase, and thus contribute to translation initiation of mRNAs with structured 5′-untranslated regions. This is an oversimplified illustration, because there are at least three signaling pathways that lie downstream of *ras*. (Adapted from Vojtek AB, Der CJ: Increasing complexity of the ras signaling pathway. J Biol Chem 273:19925–19928, 1998, with permission.)

Tumor szuppresszor gének inaktivációja

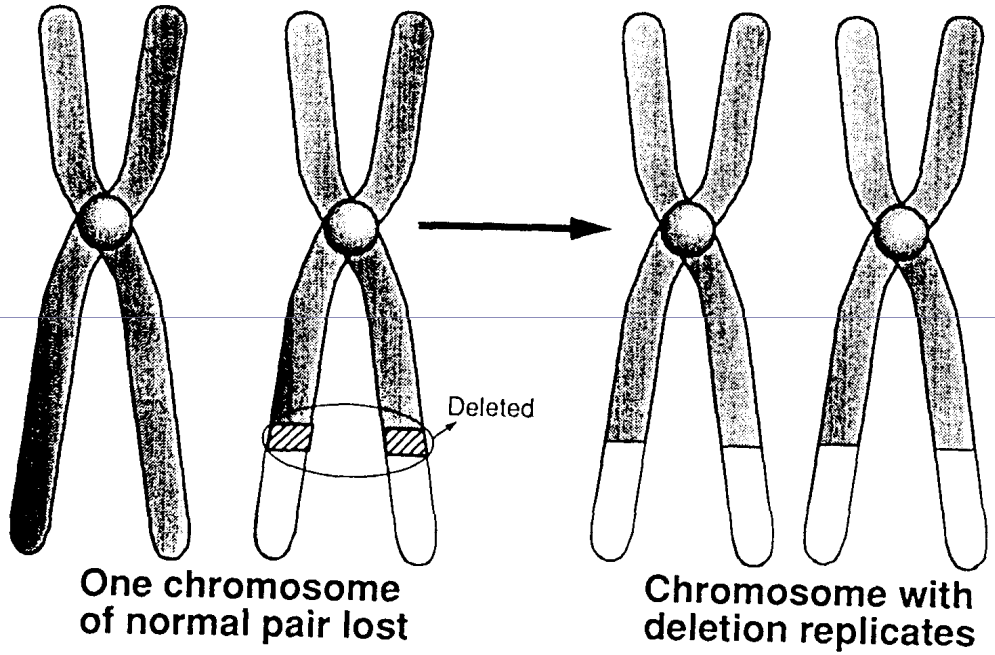
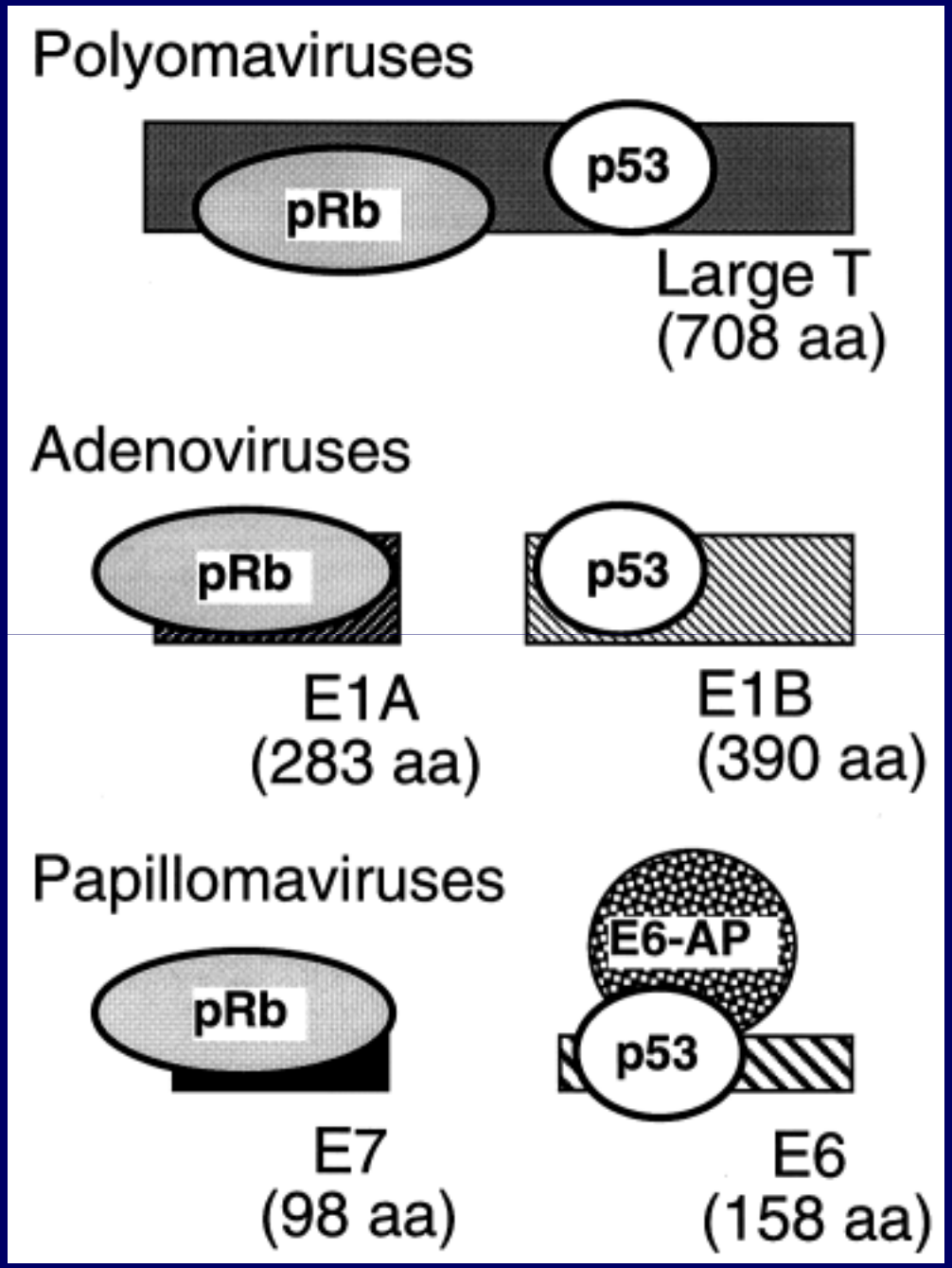


Figure 17.8. The process of somatic homozygosity. In a normal cell, there are two copies of each chromosome, one inherited from each parent. For a given suppressor gene to be inactivated, the copy must be lost from both chromosomes. This could, of course, occur by independent deletions from the two chromosomes, but in practice it is more common for a single deletion to occur in one chromosome while the second chromosome is lost completely. The remaining chromosome, with the deletion, then replicates. The cell is thus homozygous, rather than heterozygous, for that chromosome.

TABLE 17.2. *Currently Identified Tumor Suppressor Genes*

Suppressor Gene	Site	Associated Chromosome	Tumor
p-105 Rb	Nucleus	13q	Retinoblastoma
WT	Nucleus	3 different loci, llp	Wilms' tumor
NFI	Cytoplasm	17q	Neurofibroma, sarcoma
FAP	?	17q	Familial adenomatosis polyposis
p-53	Nucleus	17p	Breast cancer, small cell lung cancer, cervical cancer, bladder cancer
DCC	Cell surface	18q	Colon cancer

Virális onkogenezis



A daganatkeletkezés többlépcsős folyamat

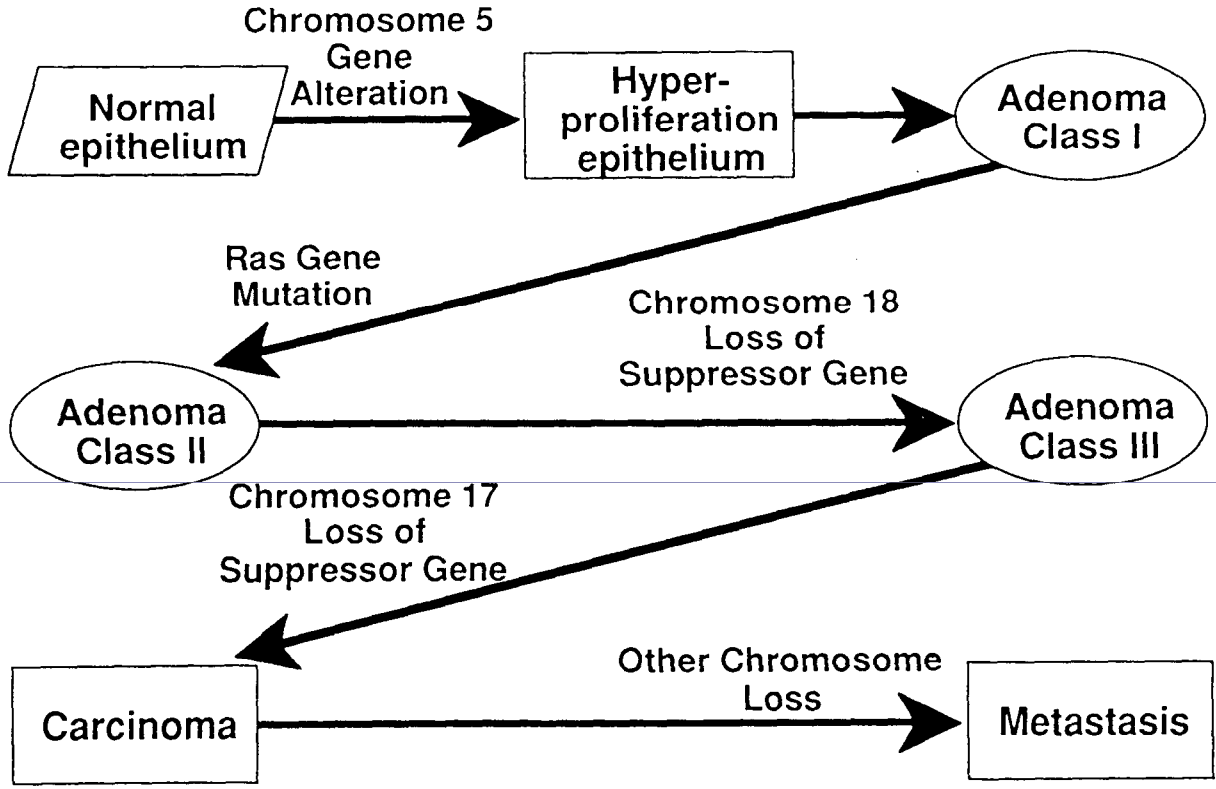
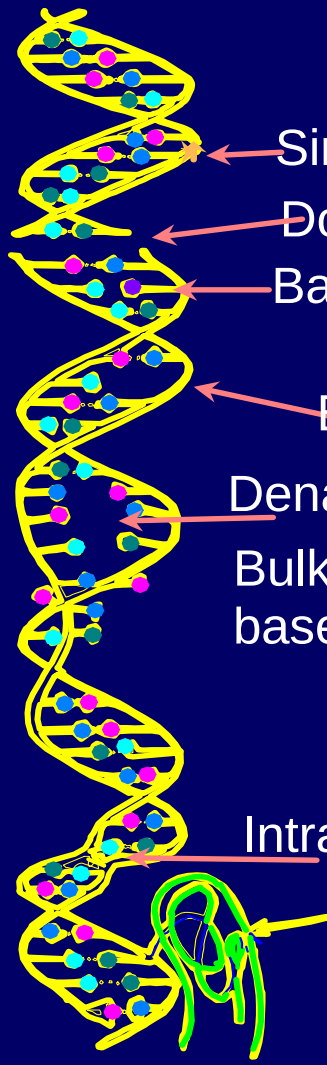


Figure 17.9. Cancer has long been thought to be a multistep process and has been described with operational terms such as *initiation*, *promotion*, and *progression*. In at least one human malignancy, namely, colon cancer, the molecular events during the progress of the disease have been identified. (Based on the work of Vogelstein.)

Ionizáló sugárzás által okozott molekuláris szintű sérülések és javításuk

Types of DNA Damage



Single strand breaks

Double strand breaks

Base damage

Base loss

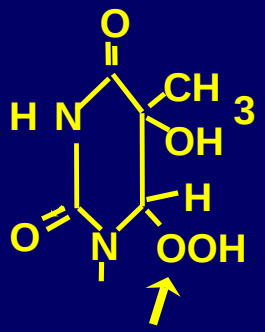
Denatured zones

Bulky lesions with base damage

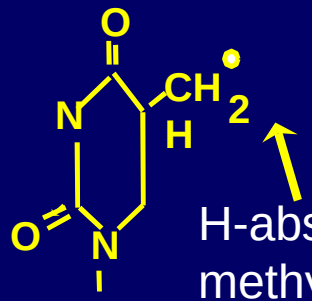
Intramolecular crosslinks

DNA-protein crosslinks

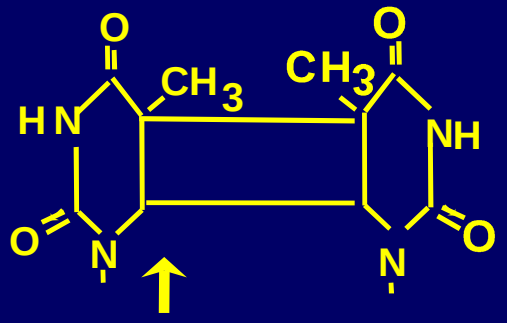
Examples of base damage (thymine)



5-hydroxy-6-hydroperoxythymine



H-abstraction at methyl of thymine



Thymine dimer (only UV)

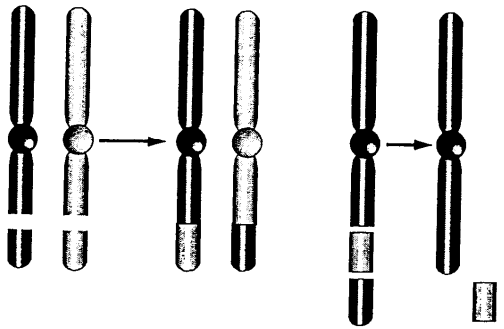


Figure 2.9. Left: Illustration of the formation of a symmetrical translocation. Radiation produces breaks in two different prereplication chromosomes. The broken pieces are exchanged between the two chromosomes, and the "sticky" ends rejoin. This aberration is not necessarily lethal to the cell. There are examples in which an exchange aberration of this type leads to the activation of an oncogene. See Chapter 19 on radiation carcinogenesis. **Right:** Diagram of a deletion. Radiation produces two breaks in the same arm of the same chromosome. What actually happens is illustrated more clearly in Figure 2.10.

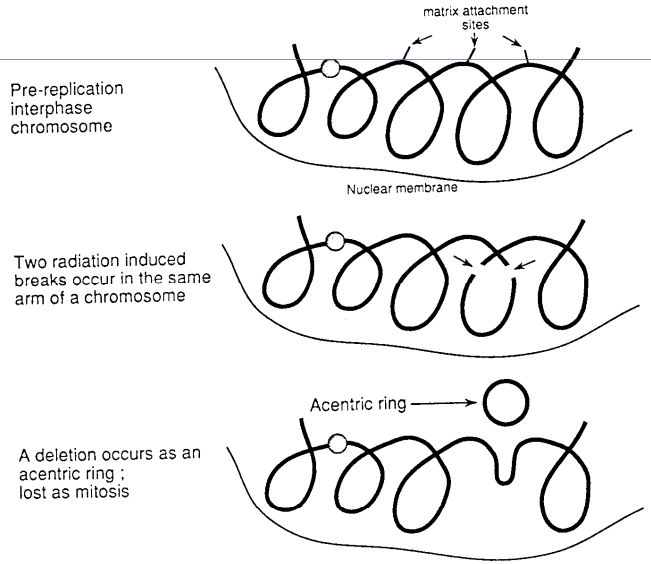


Figure 2.10. Illustration of the formation of a deletion by ionizing radiation in an interphase chromosome. It is easy to imagine how two breaks may occur (by a single or two different charged particles) in such a way as to isolate a loop of DNA. The "sticky" ends rejoin, and the deletion is lost at a subsequent mitosis because it has no centromere. This loss of DNA may include the loss of a suppressor gene and lead to a malignant change. See Chapter 19 on radiation carcinogenesis.

A molekuláris elváltozások következménye, sugárzás okozta daganatokban előforduló mutációk

Frequency of oncogenic alterations in murine tumors after *in utero* exposure to ionizing radiation

Tumors	Unirradiated	Irradiated
Lymphoid		
myc expression	28%↑	23%↑
p53 mutations	25%	13%
LOH at Acrb	40%	30%
LOH at D4Mit77	40%	23%
Liver		
H-ras expression	33%↓	20%↓
N-ras expression	33%↑	20%↑
H-ras mutations	33%	40%
LOH at Acrb	33%	40%
LOH at D4Mit77	33%	0%
Lung		
H-ras expression	50%↓	40%↓
p53 expression	50%↓	60%↓
K-ras mutations	33%	17%
LOH at Acrb	66%	0%
LOH at D4Mit77	0%	22%
Uterus		
LOH at D4Mit77	33%	25%

Incidence of the most frequent oncogenic alterations are shown. Symbols: ↓ - decreased gene expression; ↑ - increased gene expression;

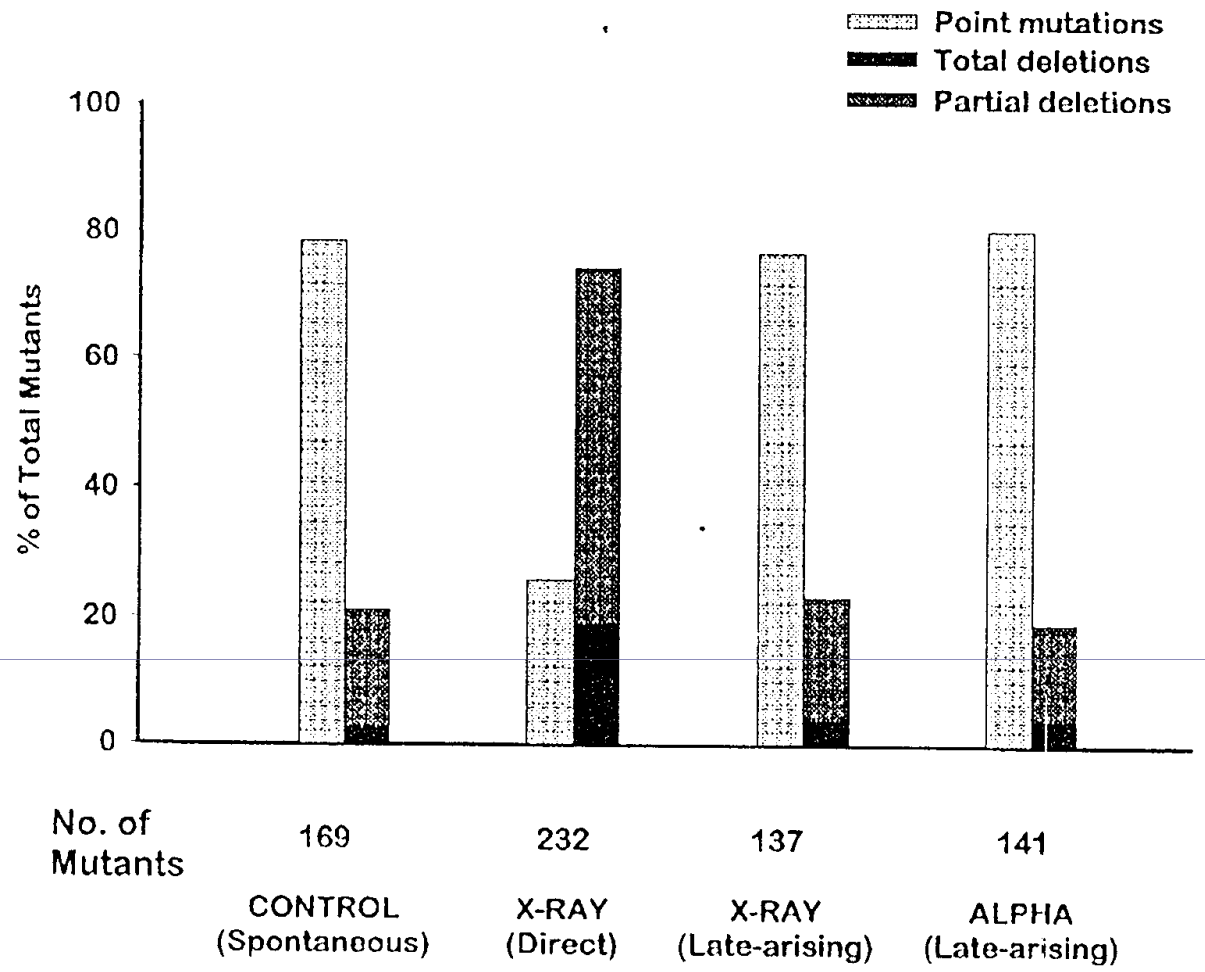


Fig. 2. Molecular structure of *HPRT* mutations in CHO cells. Direct mutations are those arising as an immediate consequence of irradiation, presumably at the site of DNA damage in the irradiated cell (Figure 3B). Late-arising mutations are those occurring in the descendants of the irradiated cell after many generations of replication (Figure 3C and D). In these experiments, mutations were analyzed in unstable clonal populations derived from single cells surviving radiation exposure and examined approximately 25 population doublings later.

Sugárzás okozta genom instabilitás és a citoplazmát ért sugárzás a hatása

Védekező mechanizmusok szerepe

mutáció≠daganat

1. apoptózis
2. adaptáció
3. immunrendszer

A küszöbdózis nélküli daganatkeletkezés kritikája

Összefoglalás

1. az ionizáló sugárzás dózisfüggően daganatot okozhat

2. nincs a sugárzásra specifikus mutáció a kialakult daganatokban

3. nem minden mutáció okoz daganatot

4. a daganatkeletkezés küszöbdózis nélküli lineáris modellje jól használható sugárvédelmi szempontokból, de valószínűleg túlbecsüli a sugárhatásra kialakuló daganatok számát.