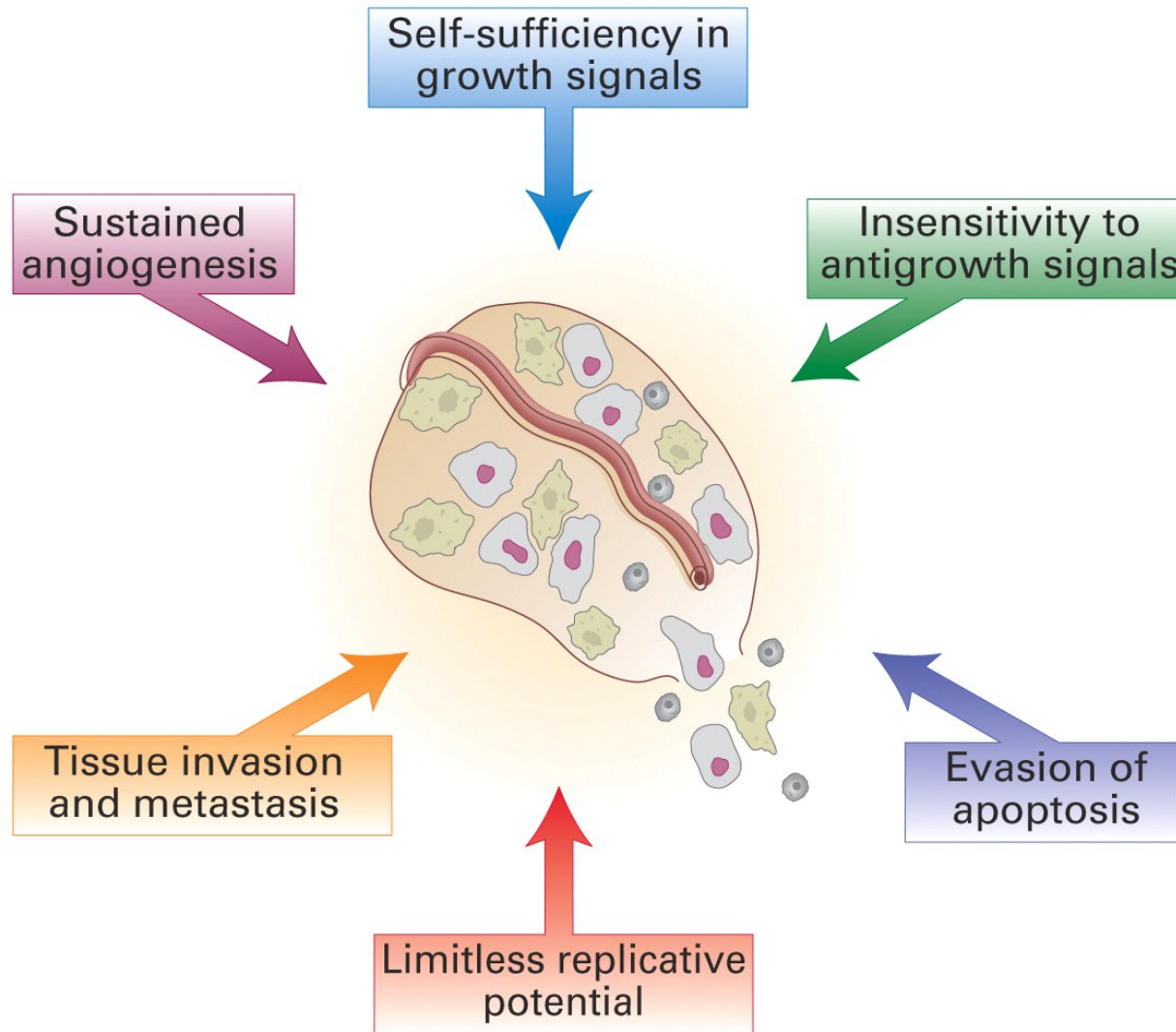


Chemical Carcinogenesis: Initiation, Promotion and Progression

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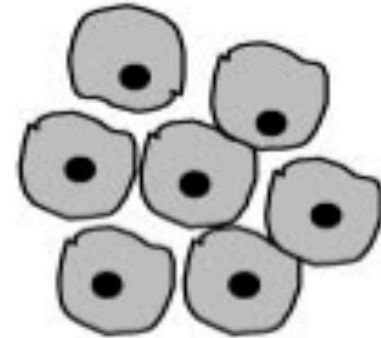
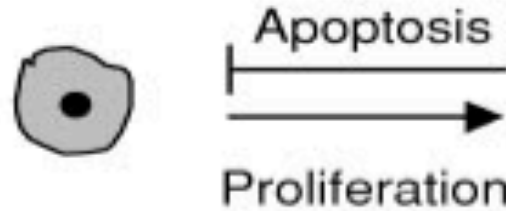
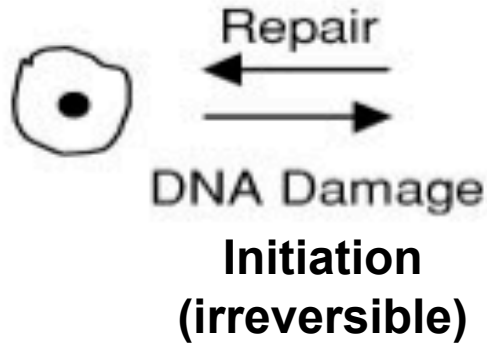
Characteristics of Cancer



Normal Cell

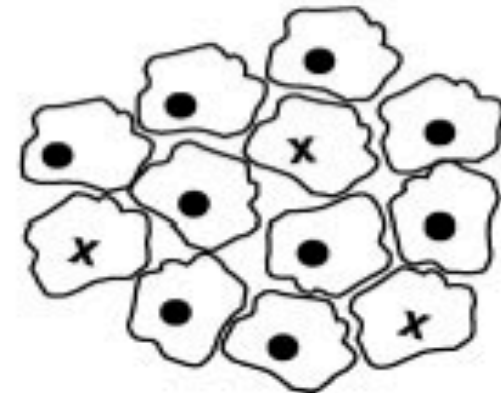
Initiated Cell

Preneoplastic Focal Lesion



Promotion (reversible)

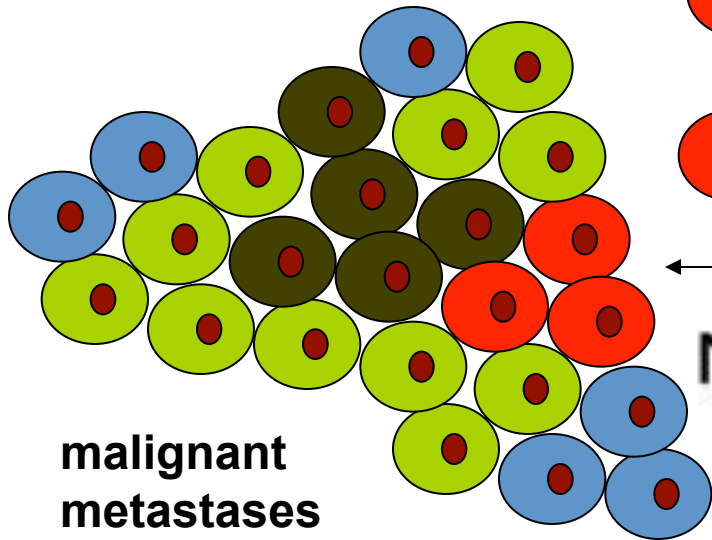
Proliferation



More mutations

Progression (irreversible)

Neoplasia



Different Steps of Carcinogenesis

Initiation: Mutation in one or more cellular genes controlling key regulatory pathways of the cell (irreversible)—must be a heritable DNA alteration.

Promotion: selective growth enhancement induced in the initiated cell and its progeny by the continuous exposure to a promoting agent.

Progression: results from continuing evolution of unstable chromosomes; further mutations from genetic instability during promotion—results in further degrees of independence, invasiveness, metastasis, etc.

Initiation

- Initiation is the induction of a mutation in a critical gene involved in the control of cell proliferation.
- As with mutational events, initiation requires one or more rounds of cell division for the “fixation” of the process.
- The metabolism of initiating agents to non-reactive forms and the high efficiency of DNA repair of the tissue can alter the process of initiation.
- Initiation is irreversible although the initiated cell may eventually die during the development of the neoplasm.

Types of mutations

Chemical carcinogens can cause:

1. Point mutations- the replacement of a single nucleotide base with another nucleotide.
2. Frameshift mutations- addition or deletion of a nucleotide such that the protein sequence from that point onward is altered.
3. Chromosomal aberrations- any change in the normal structure or number of chromosomes
4. Aneuploidy- chromosome number is not a multiple of the normal haploid (23)
5. Polyploidy- more than twice the haploid number of chromosomes

Mechanisms of DNA Repair

The persistence of chemically-induced DNA adducts is predominantly the result of failure of DNA repair, due to either:

- carcinogen-induced mutational inactivation of DNA repair enzymes.
- failure of the DNA repair mechanisms to recognize carcinogen-induced mutation.

Table 8-7

Types of DNA Repair

1. Direct reversal of DNA damage
Alkyltransferases
2. Base excision repair
Glycosylase and AP endonuclease
3. Nucleotide excision repair
T-T, C-C, C-T repair
“Bulky” adduct repair
4. Double-strand-break repair
Homologous recombination (HR)
Nonhomologous DNA end joining (NHEJ)
5. Mismatch repair
Repair of deamination of 5-Me cytosine
Repair of mismatches in DNA due to defective repair, etc.

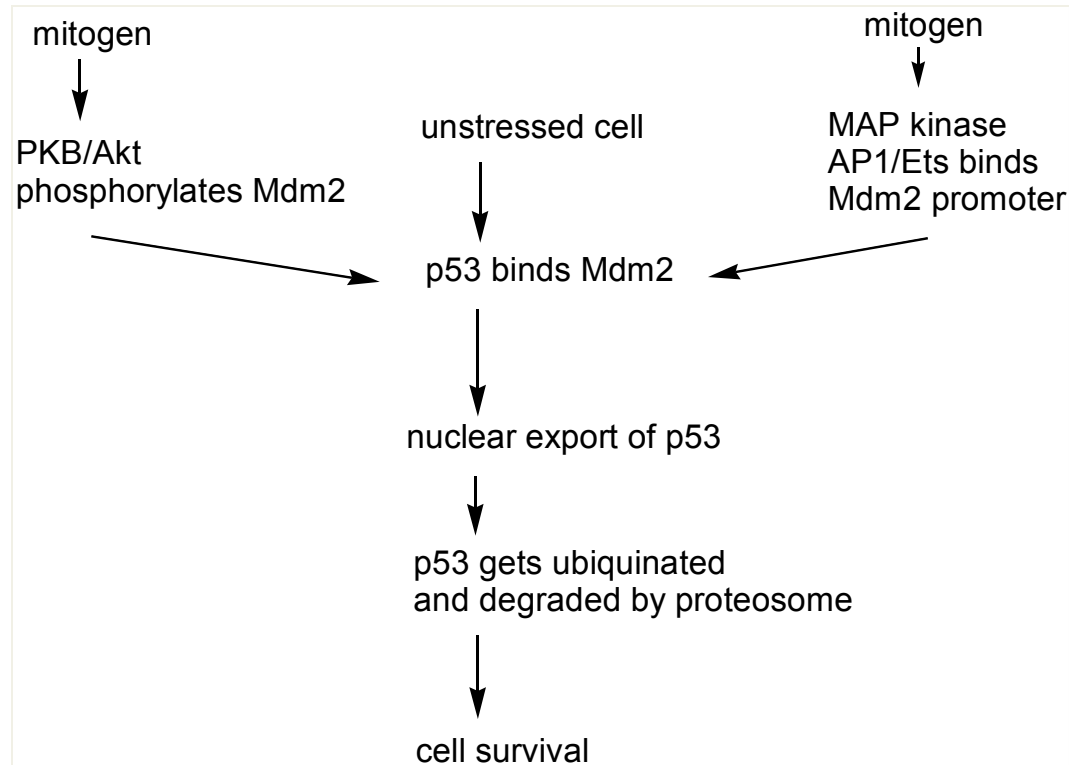
SOURCE: Modified from Myles and Sancar (1989) and from Lieber (1998), with permission.

Targets of Initiation

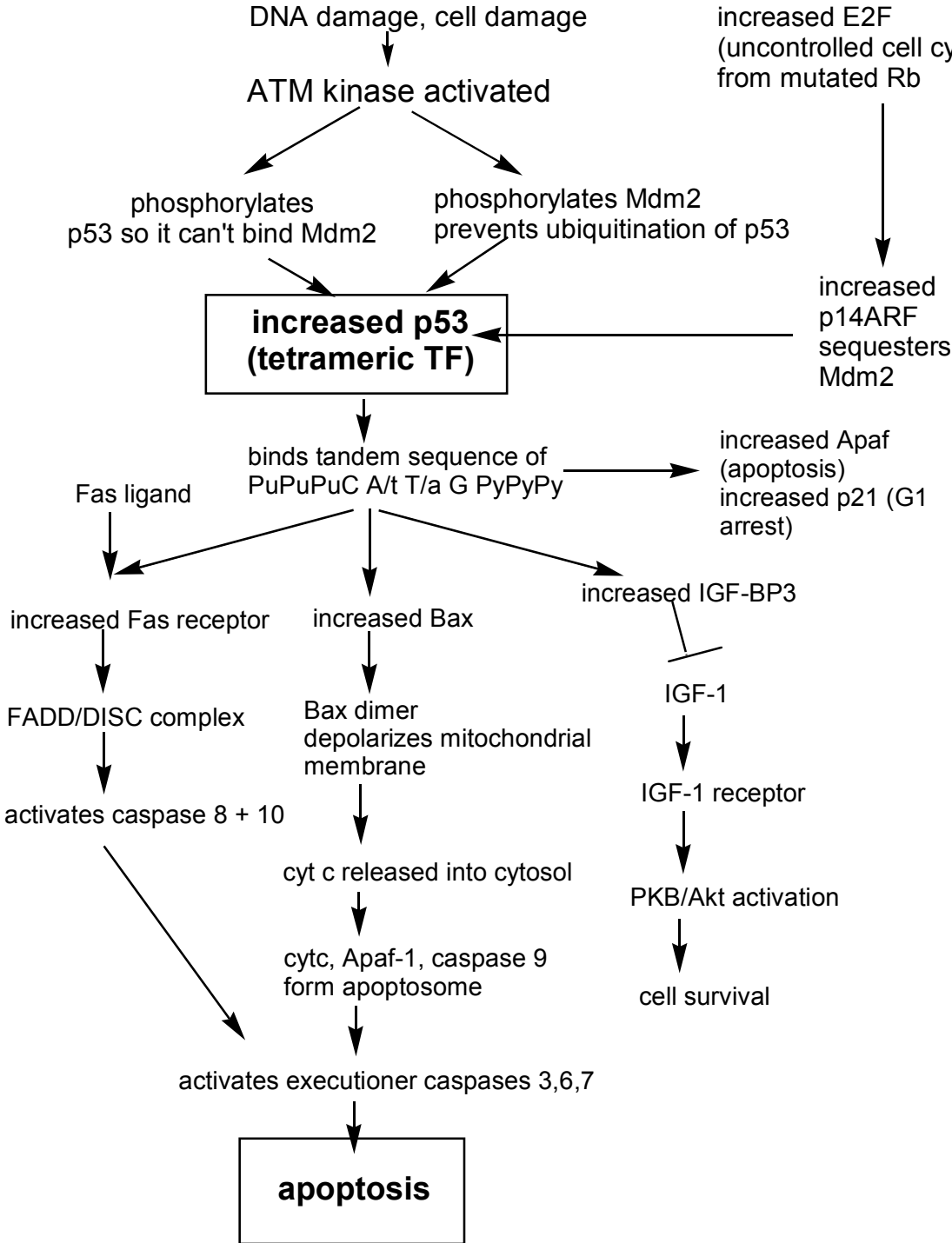
Chemical carcinogens initiate cells via:

1. Mutational activation of oncogenic (proliferative) pathways (e.g. growth factor receptors and downstream signaling proteins, proteins involved in cell cycle checkpoints).
2. Mutational inactivation of apoptotic (cell death) pathways (e.g. growth inhibitory receptors, proteins involved in apoptosis, tumor suppressors).
3. Mutational inactivation of DNA repair mechanisms (e.g. BER, NER, etc).
4. Mutational inactivation of antioxidant response (e.g. SOD).

Tumor suppressor p53 signaling



- p53 is an important tumor suppressor (transcriptional factor) that controls cell cycle, apoptosis, DNA repair mechanisms.
- Mdm2 is a negative regulator of p53 that functions both as an E3 ubiquitin ligase and an inhibitor of p53 transcriptional activation.

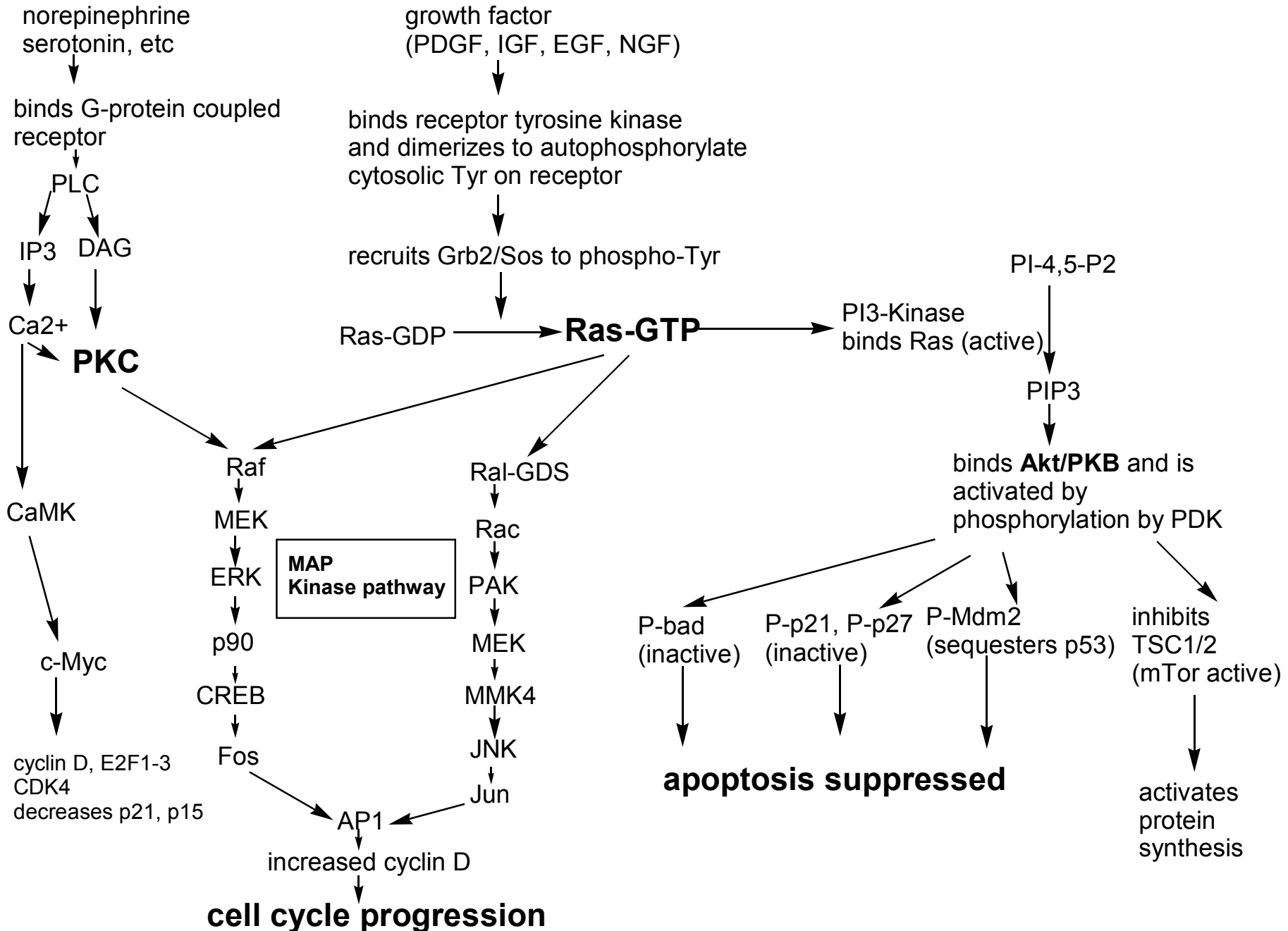


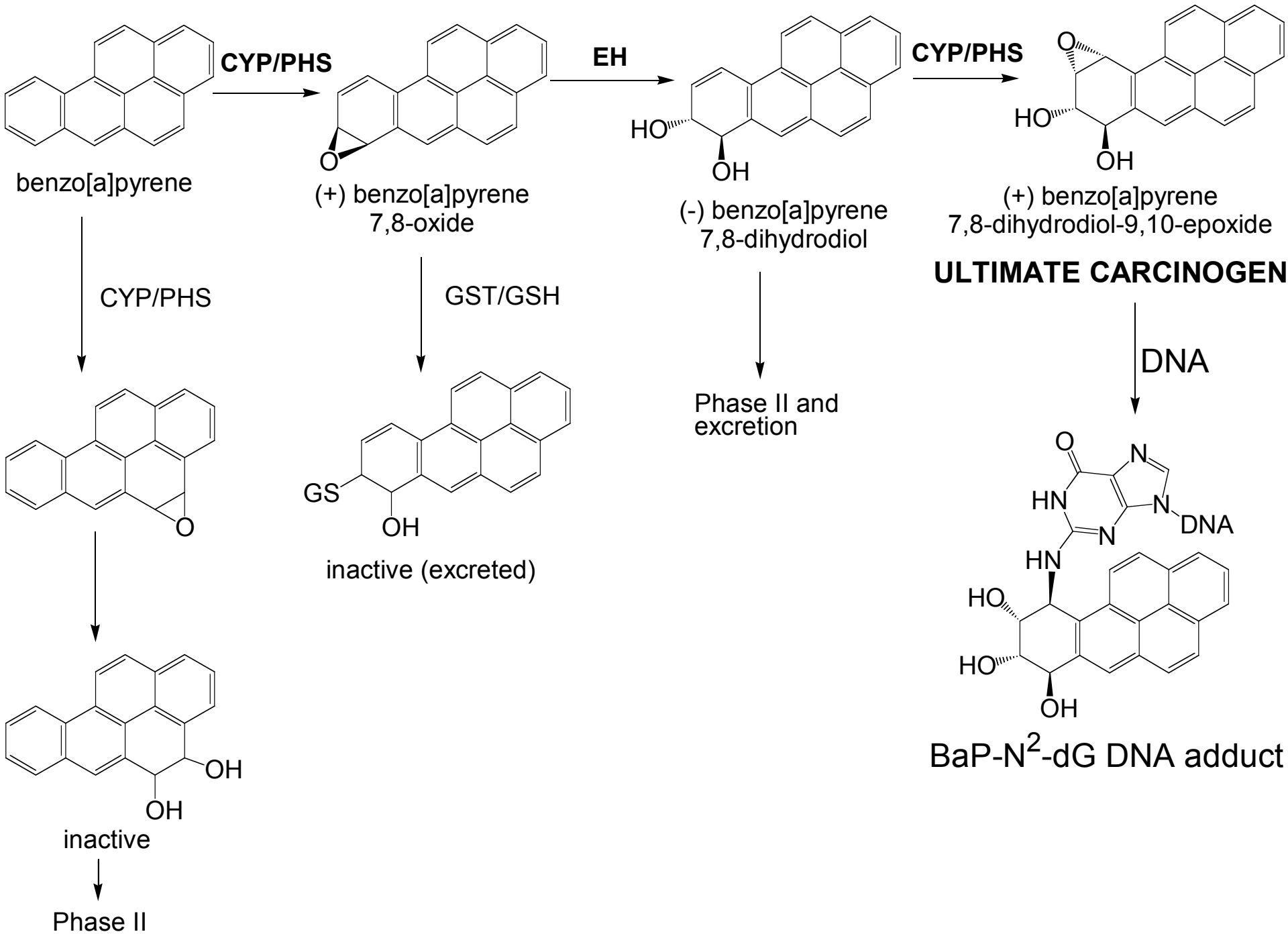
p53—tumor suppressor:

Mutated in most cancers.

Carcinogens often mutationally inactivate p53 as well as proteins that control p53 function (e.g. Mdm2, p14)

Ras oncogene: involved in control of cell cycle progression and apoptosis

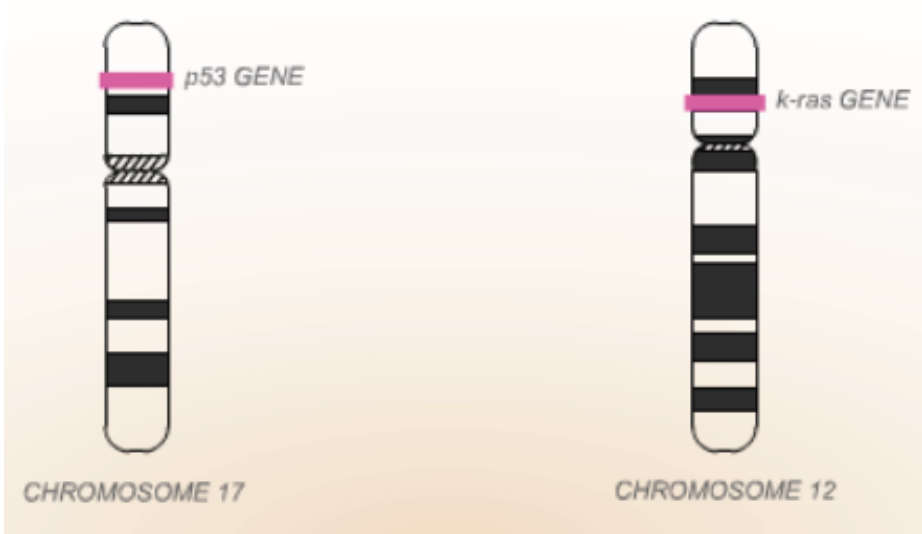




Benzopyrene Leads to Mutations in K-Ras and p53 in the Genomic Loci Found to be Mutated in Smoking-Induced Lung Cancers

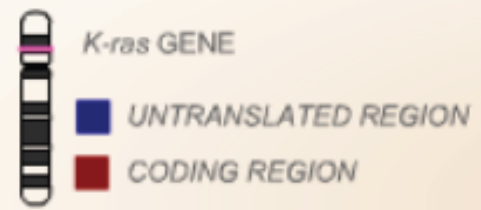


- ***K-Ras and p53*** are the two ***oncogenes*** most frequently mutated in smoking-related lung cancers
- If not corrected by the cell's DNA repair mechanism, this guanine “adduct” is misread as a thymine by the DNA polymerase that copies chromosomes during replication
- Ultimately, the original G—C base pair may be replaced by a T—A base pair, a mutation called a transversion
- Cells treated with Benzopyrene show the same spectrum of G—T transversions as found in the K-RAS and p53 of smokers.
- These mutational “hot spots” map well to the guanine binding sites of BaP epoxide

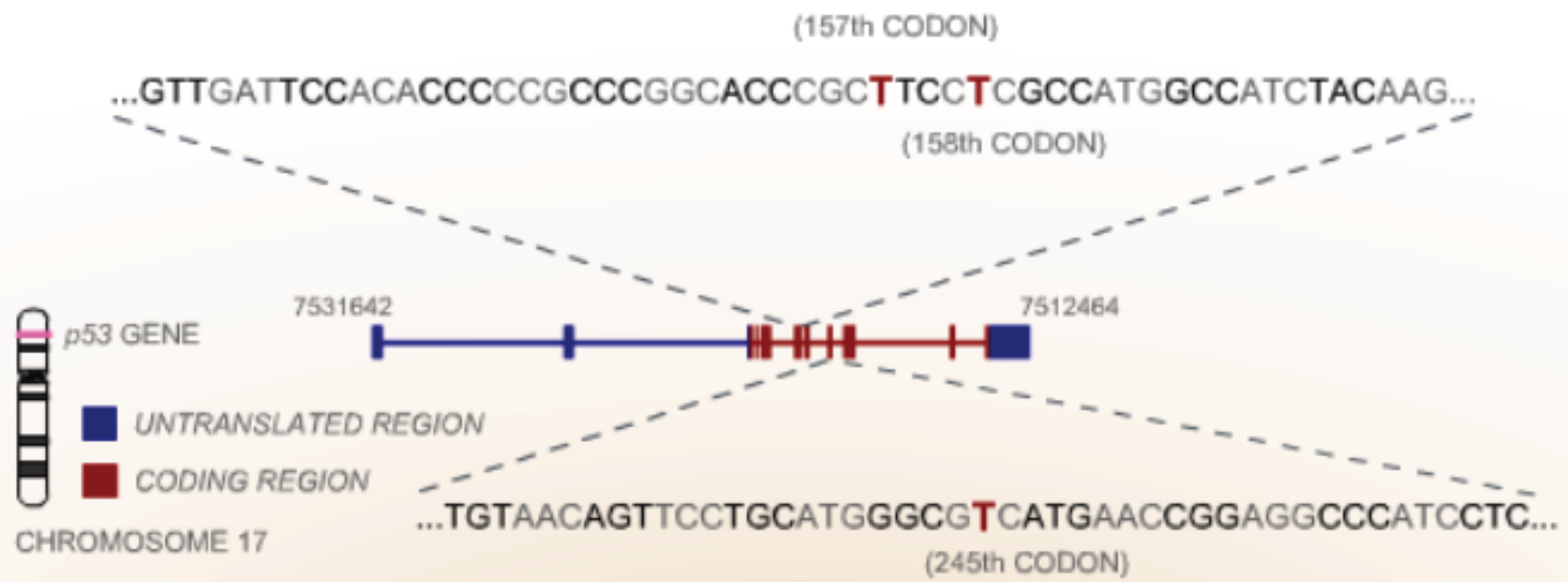
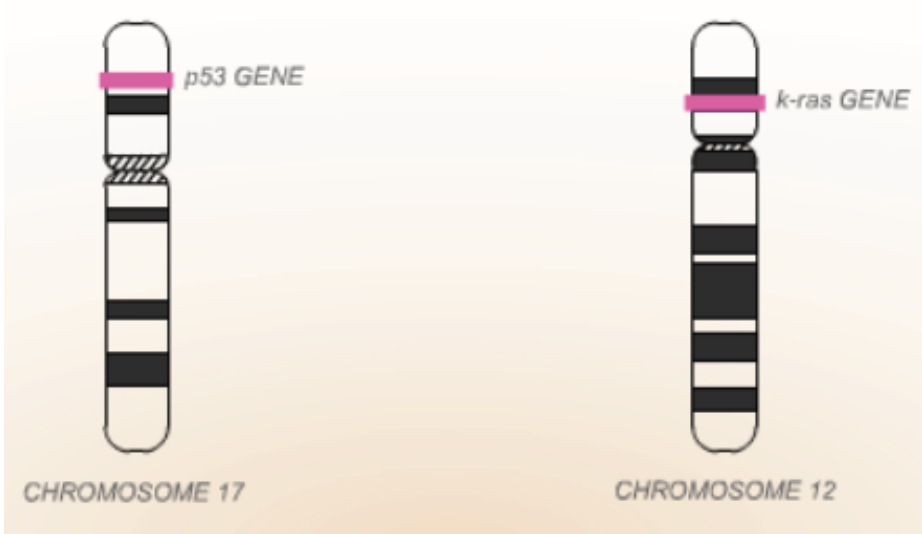


(12th codon)

...ATGACTGAATATAAACTTGTGGTAGTTGGAGCT**T**GTGGCGTAGGCAAGAGTGCCTTGACG...



CHROMOSOME 12



Promotion

Promotion

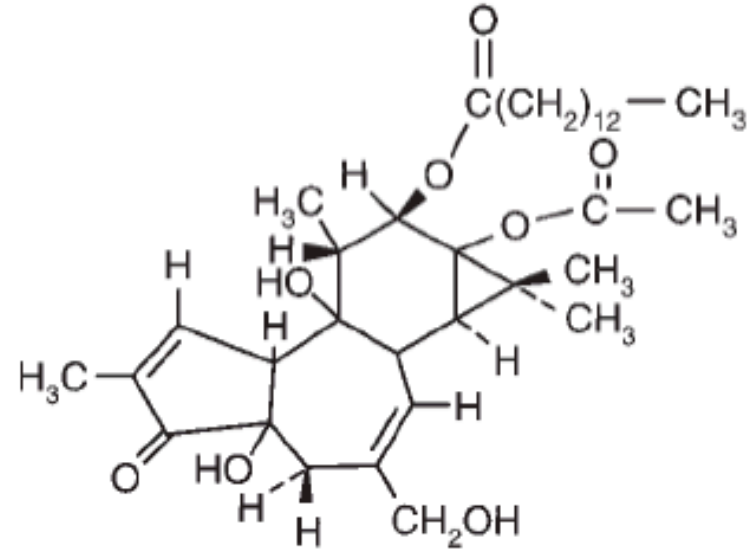
- Epigenetic event—change in gene expression without change in DNA.
- Mitogenic (Not mutagenic) Stimulates proliferation. Causes both mutated and normal cells to proliferate.
- Enhances the effect of the genotoxic initiating agent by establishing clones of initiated cells.
- Long delay possible between administration of initiating agent and promoting agent.
- Promotion is reversible.

Promoters

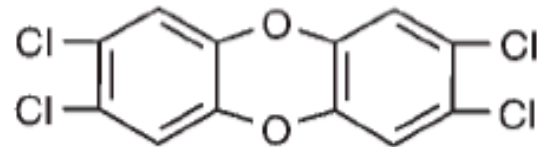
1. Reactive Oxygen Species (ROS) and redox active xenobiotics and metals
2. Phorbol esters (e.g. TPA)
3. Polycyclic aromatic compounds (e.g. Dioxin)
4. Peroxisome Proliferators (oxidized fats)
5. Endocrine Disruptors (estradiol, DES)

Structures of Representative Promoters

TPA and other phorbol esters activate protein kinase C, which leads to signal transduction pathways that increase DNA replication, cell division



TetradeCANOYL phorbol acetate (TPA)



2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

TCDD (dioxin) activates aryl hydrocarbon receptor (AhR) and induces the expression of cytochrome P450 → increases oxidative stress → can oxidatively activate oncogenic pathways (e.g. RAS)

Endocrine Receptors and Carcinogenesis

Endocrine disruptors are involved in breast, ovarian, colon, prostate cancers.

1. ER β /ER α (estrogen receptors) ratio is decreased in cancers (ligands include estradiol); ERs are transcription factors.

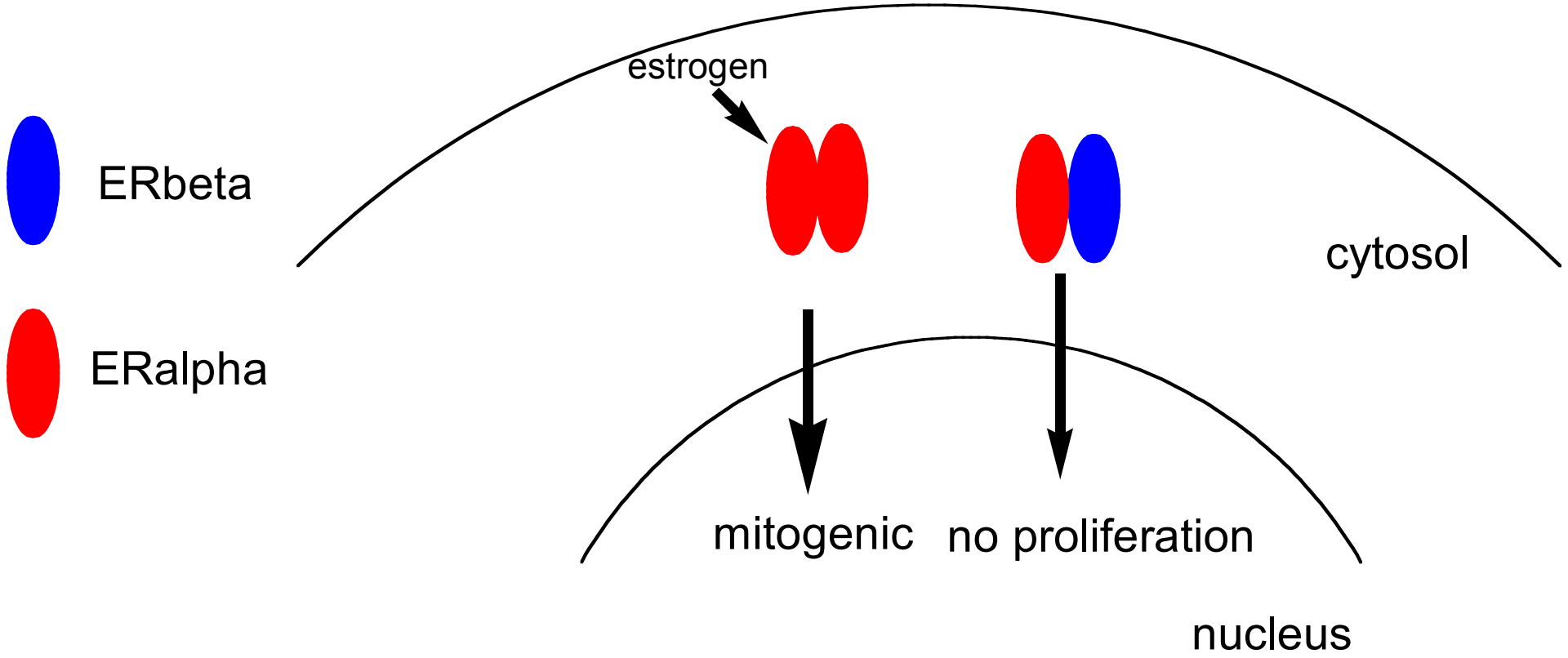
2. ER β inhibits ER α

a. ER α -ER α dimerization (homodimer) leads to mitogenic activation.

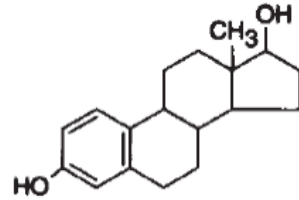
b. ER β -ER α dimerization (heterodimer) leads to an inactivation.

3. Androgen Receptor (prostate) (AR) can also homodimerize with AR leading to mitogenic activation; AR can heterodimerize with ER β to cause growth arrest (prostate also dependent on estrogenic signals).

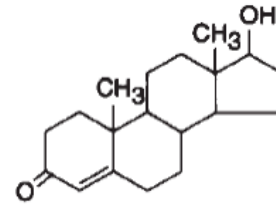
Estrogen Receptor Interactions



Examples of Endocrine Disruptors

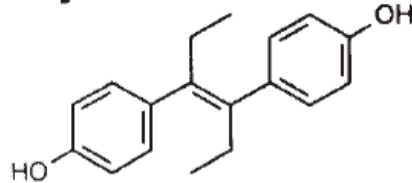


17 beta-Estradiol

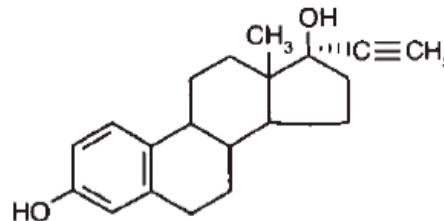


Testosterone

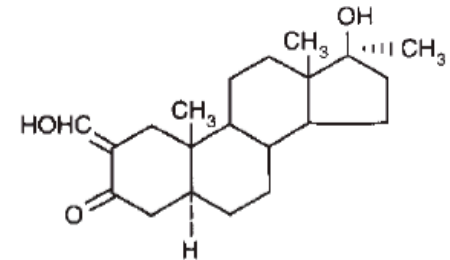
B. Synthetic



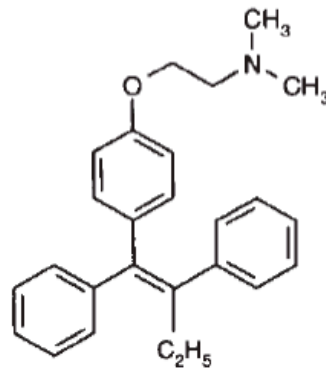
Diethylstilbestrol



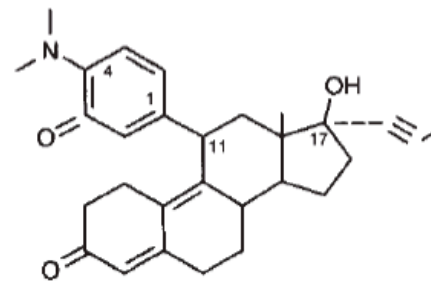
Ethinyl Estradiol



Oxymetholone



Tamoxifen



RU 486

Other examples include dioxin, polychlorinated biphenyls (PCBs), DDT, bisphenol A (BPA) and atrazine.

Progression

Mechanisms of Progression

Progression is an irreversible process and leads to metastasis.

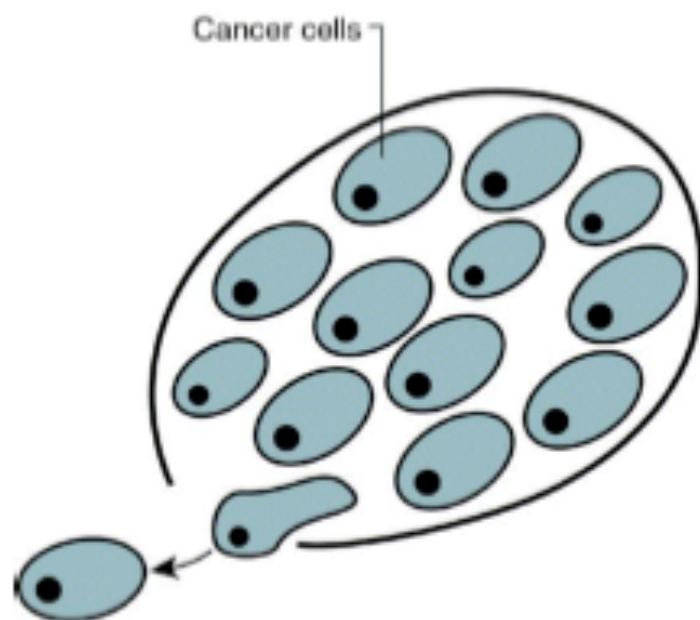
Progression requires:

1. Further mutations from genetic instability (chromosomal instability) during promotion.
2. Recruitment of inflammatory immune cells to the tumor.
3. The tumor cell acquiring “wound-healing” characteristics (secretion of chemo-attractants to attract inflammatory immune cells, angiogenesis factors, proteases, etc).

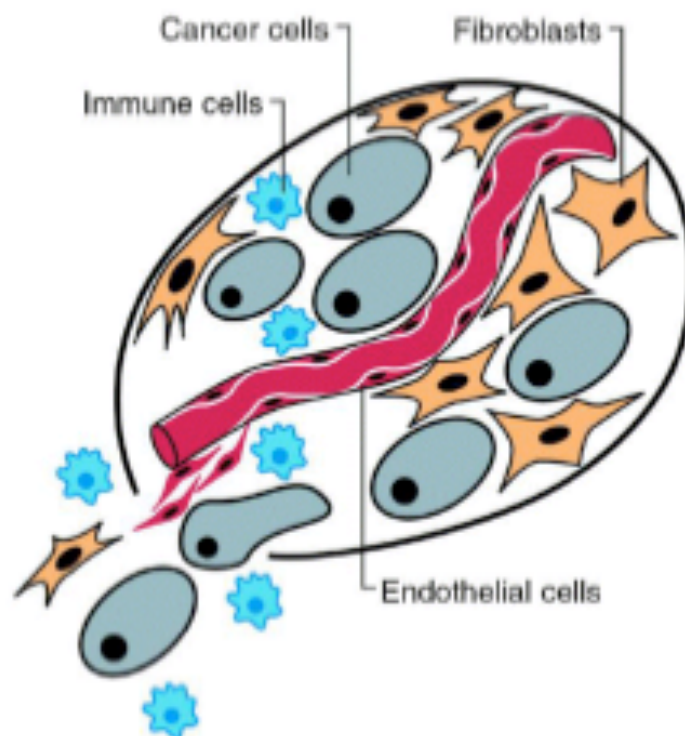
Examples of progressor agents: inflammation, asbestos fibers, benzene, benzoyl peroxide, other peroxides, oxidative stress, inflammation

A Changing View of Cancers

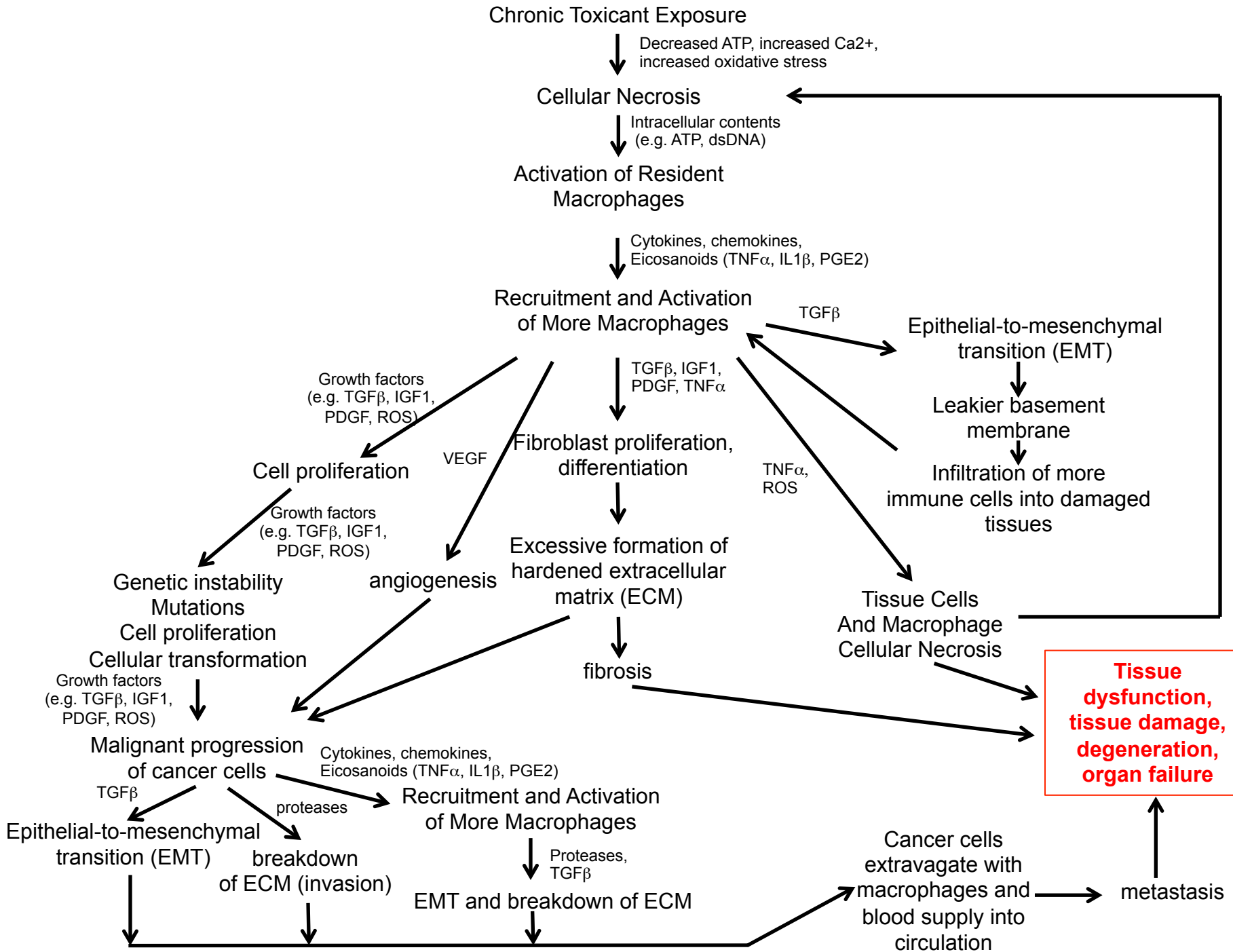
The 'old' view



The 'new' view



Cancers are composed of different types of cells that interact with each other (heterotypic interactions) to facilitate the growth and spread of the tumor mass.



Inflammation and Cancer

- Inflammation acts at all stages of tumorigenesis
- It may contribute to tumor initiation through mutations, genomic instability
- Inflammation activates tissue repair responses, induces proliferation of premalignant cells, and enhances their survival
- Inflammation also stimulates angiogenesis, causes localized immunosuppression, and promotes the formation hospitable microenvironment in which premalignant cells can survive, expand, and accumulate additional mutations
- Inflammation also promotes metastatic spread.

