

Lecture 20 Cancer Biology

Outline

- I. The nature of Cancer
- II. Properties of cancer
- III. Cause of cancer
- IV. Cancer critical genes
- V. Multi-step tumorigenesis
- VI. Cancer stem cells
- VII. Tumor metastasis
- VIII. Cancer treatment

I: Nature of tumor

What is tumor?

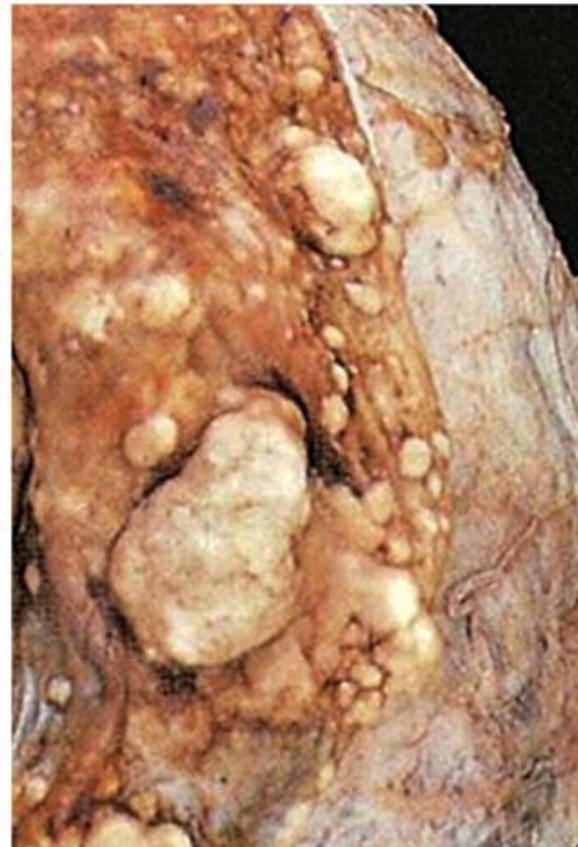
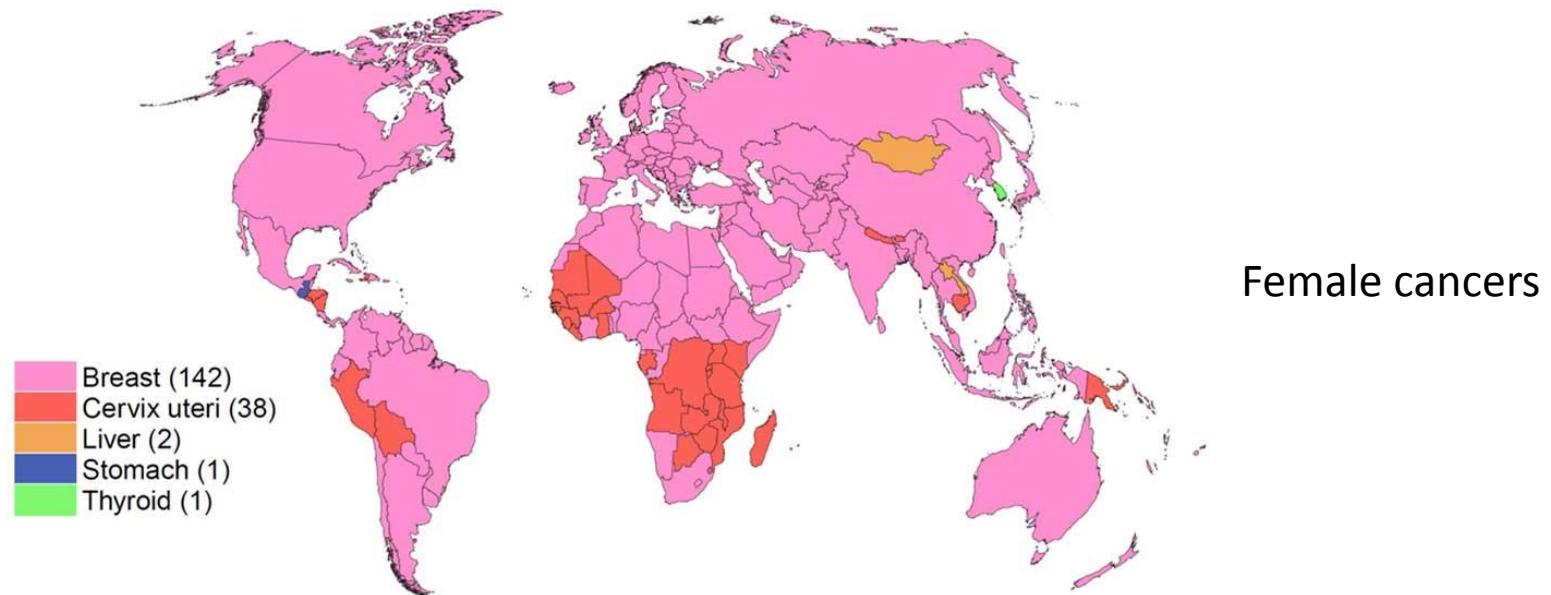
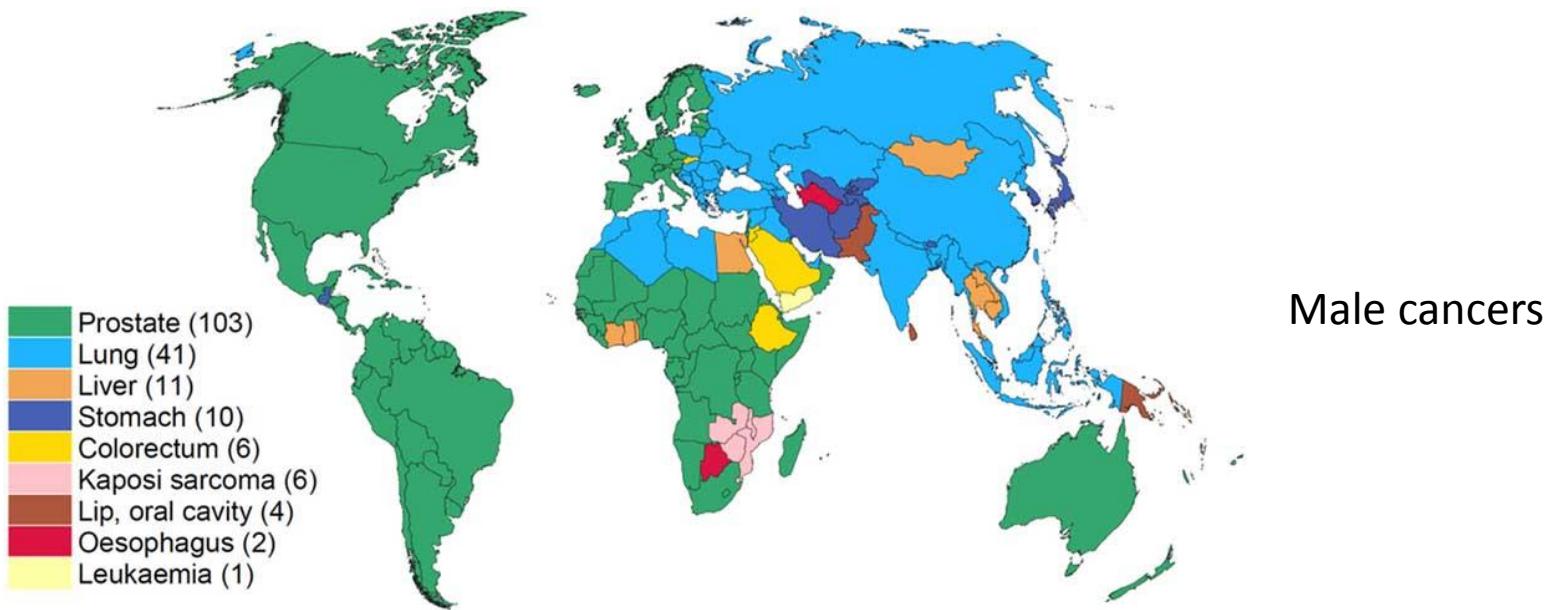
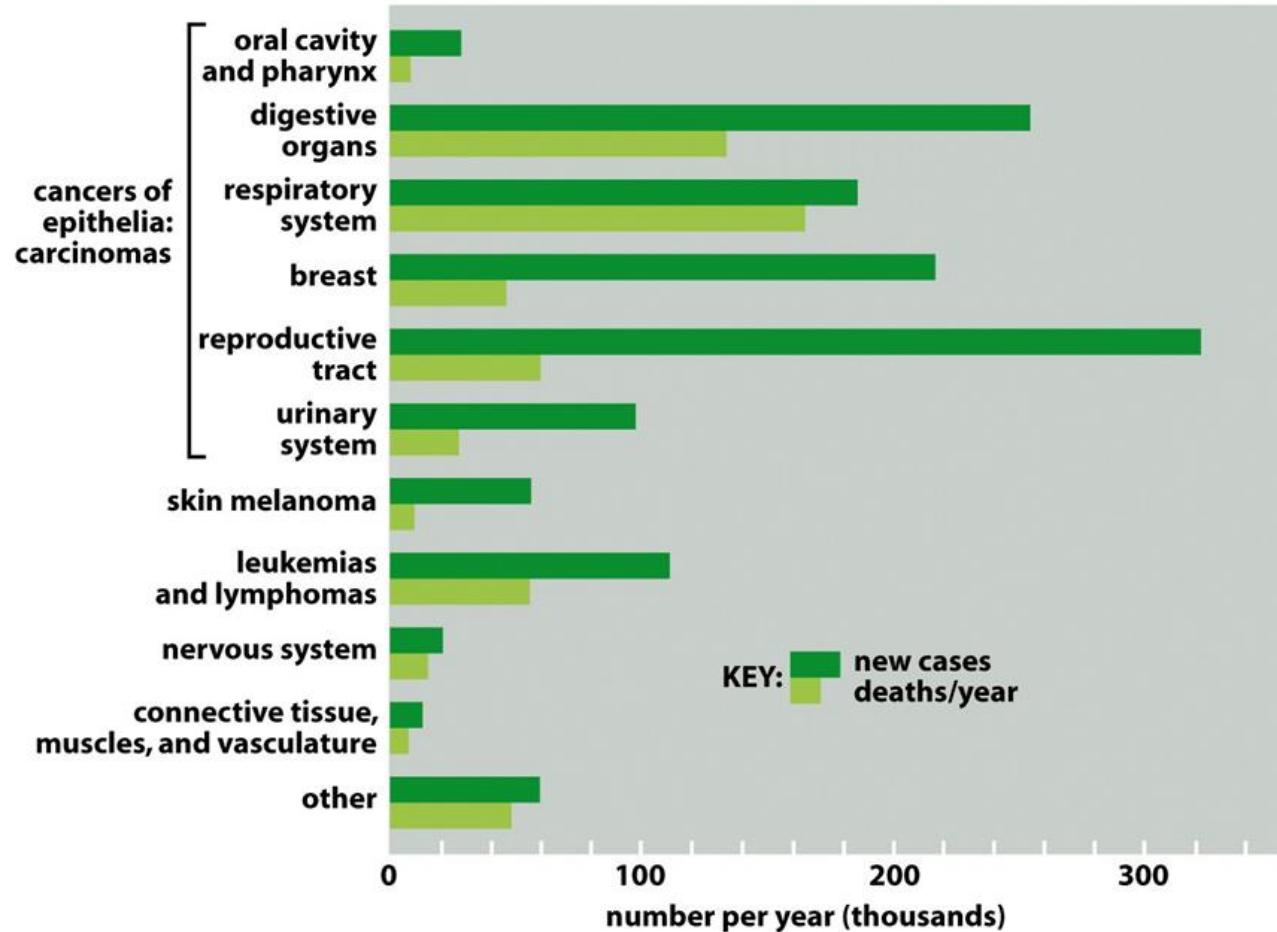


Figure 2.2 The Biology of Cancer (© Garland Science 2014)

World wide cancer statistics



Incidence and death of cancer



In the US

What is cancer?

- Cancer cells are cells that grow beyond limitation:
 - (1) Cells grow out of control, has sustaining proliferating potential
 - (2) Be able to invade into distant organs

Primary tumor, metastasis tumor; benign tumor, malignant tumor

- primary tumor versus metastasis

Primary tumor: cancer that had begun in original site

Metastasis: new settlement of tumor derived from primary tumor

- Benign tumor versus malignant tumor

Benign tumor : tumors that grow locally but no invasion

Malignant tumor: tumors invade into distant organs

Tissue images of cancer

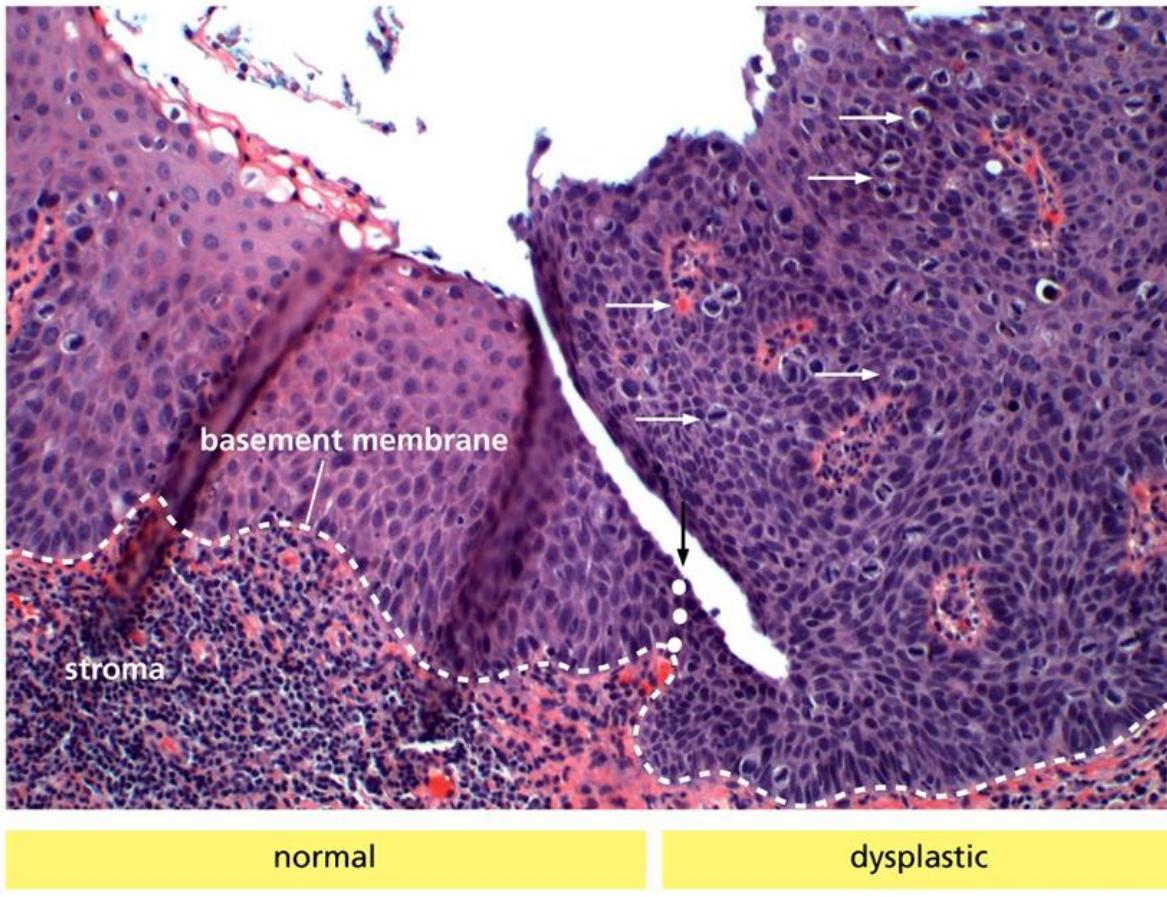


Figure 2.15 The Biology of Cancer (© Garland Science 2014)

Cervix intraepithelia neoplasia (CIN)

- Normal versus hyperplasia epithelium in the duct of mammary gland

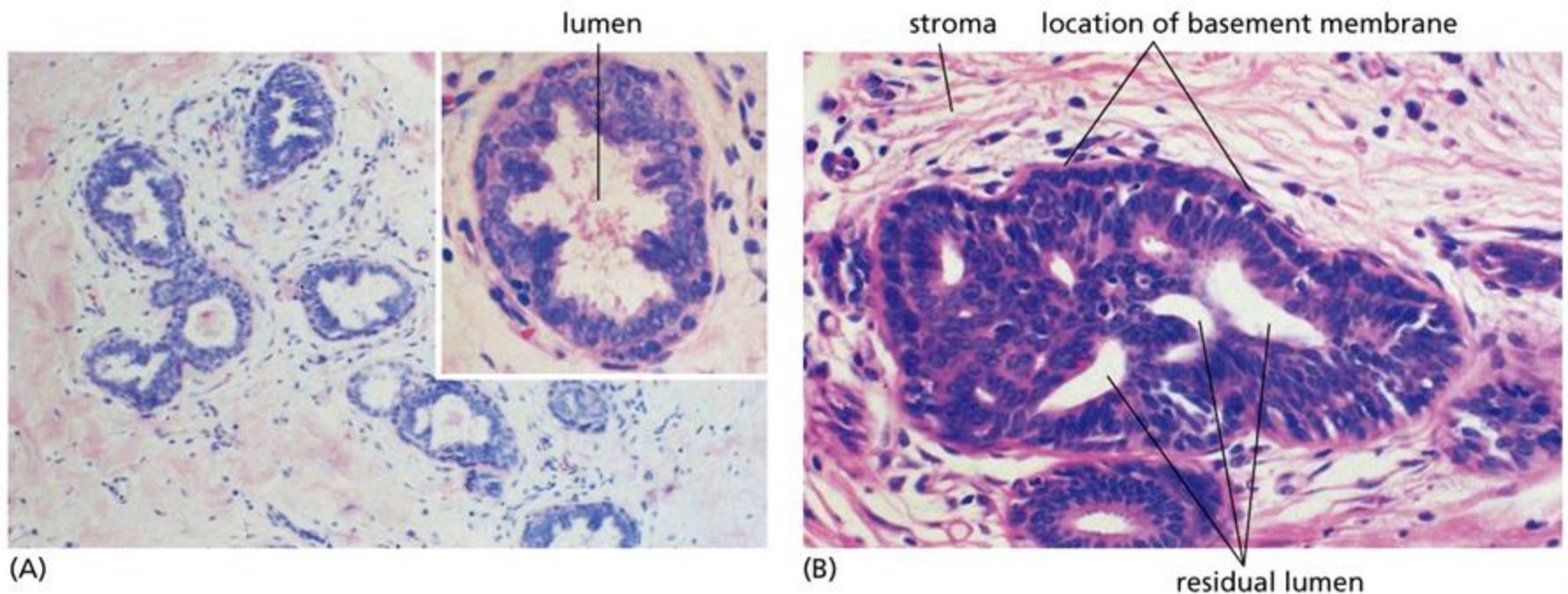
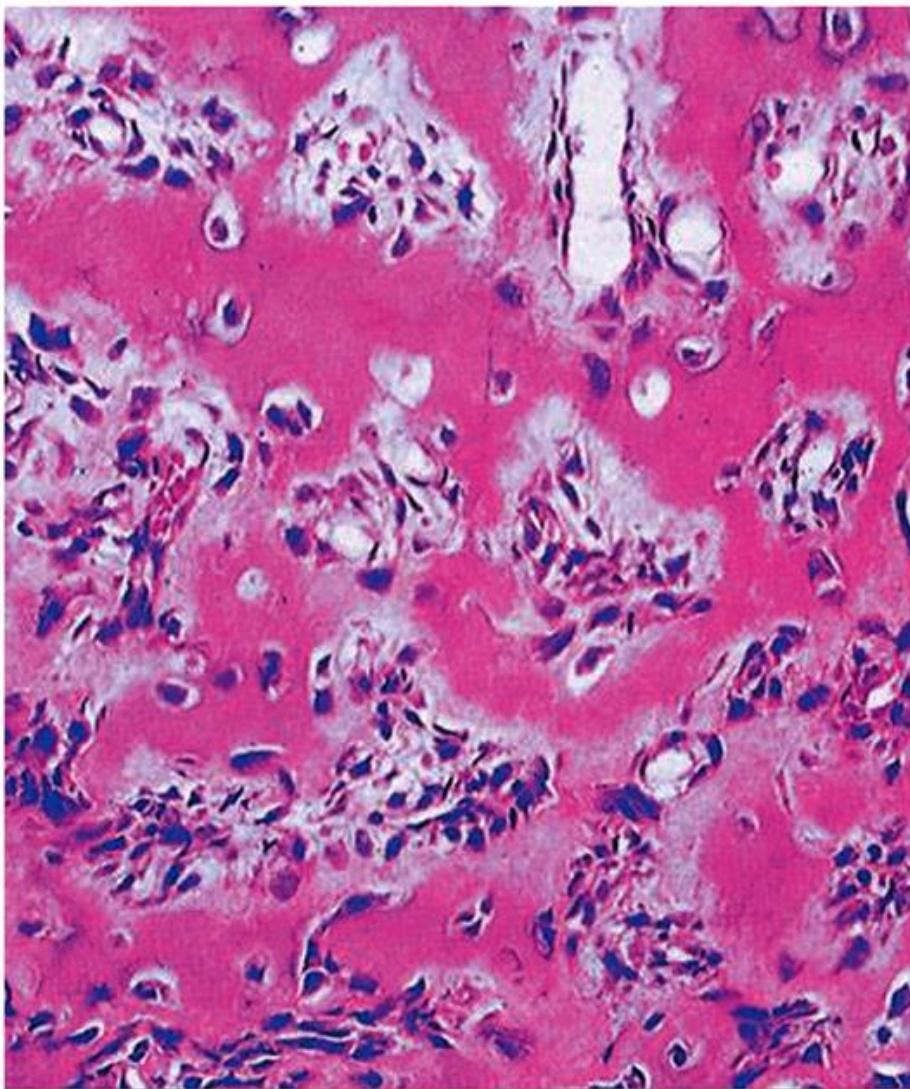


Figure 2.13 The Biology of Cancer (© Garland Science 2014)

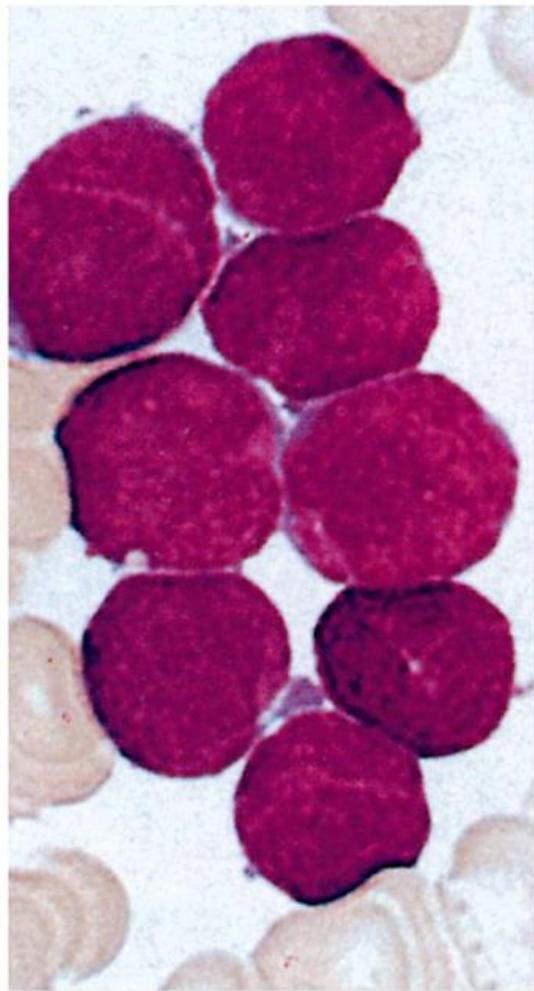
Osteosarcoma



Osteoblast proliferation
Pink: bone matrix

Hematopoietic malignancies

ALL(acute lymphocytic leukemia)



AML(acute myelogenous leukemia)

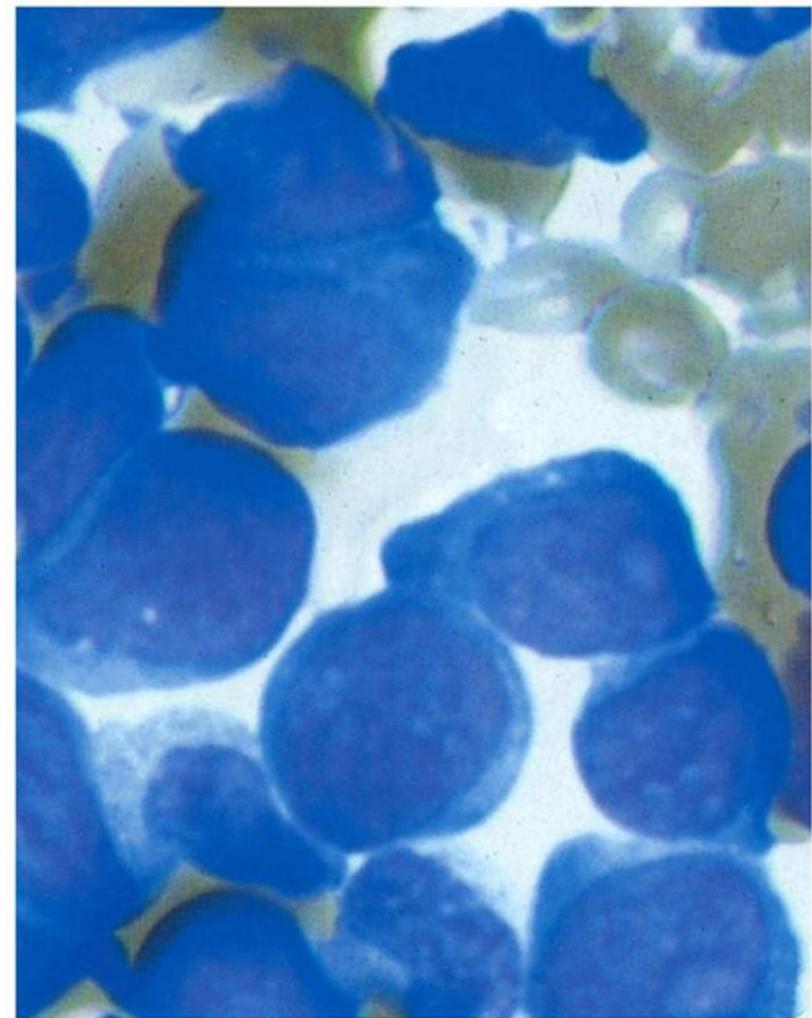
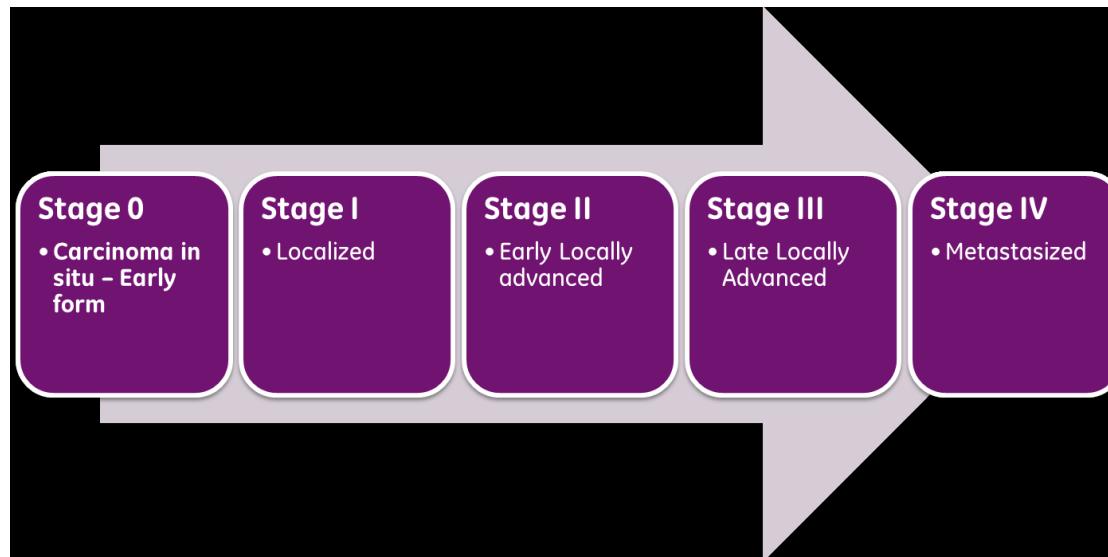


Figure 2.8a The Biology of Cancer (© Garland Science 2014)

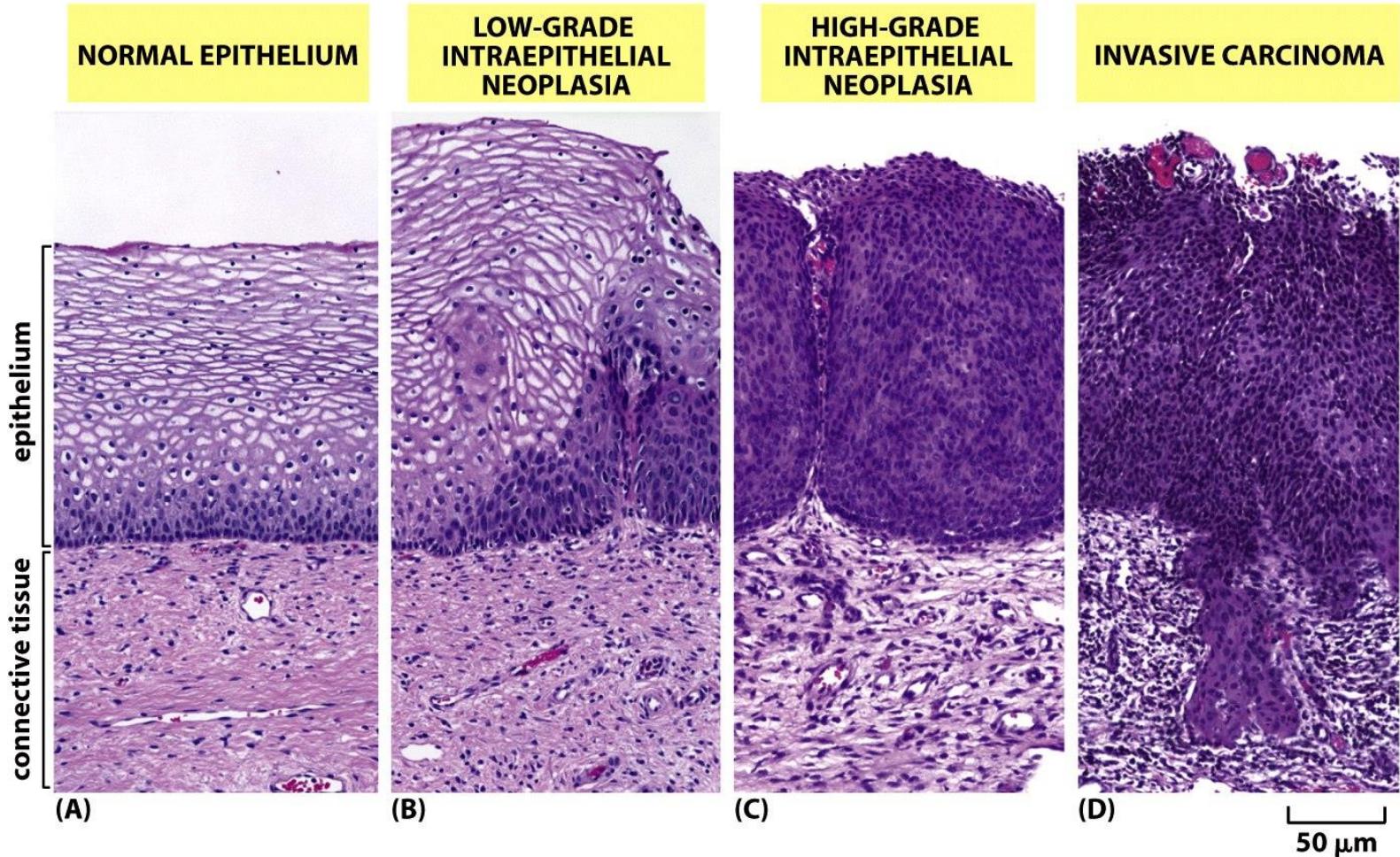
Figure 2.8b The Biology of Cancer (© Garland Science 2014)

Categories and stages of tumor

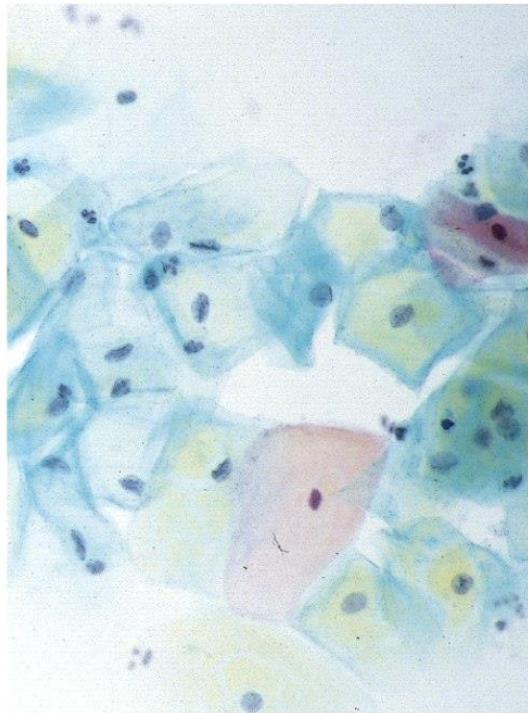
- Carcinoma : major type, epithelial origin
- Sarcoma: connective tissue origin
- Leukemia/lymphoma: blood cell origin
- Neurological tumor: brain and nerve tissue



Developmental stages of carcinoma

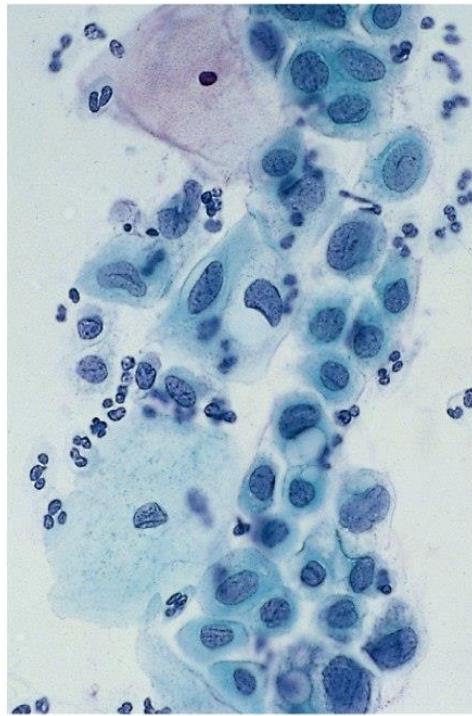


Tumor cells have increase nuclear/cytoplasm ratio

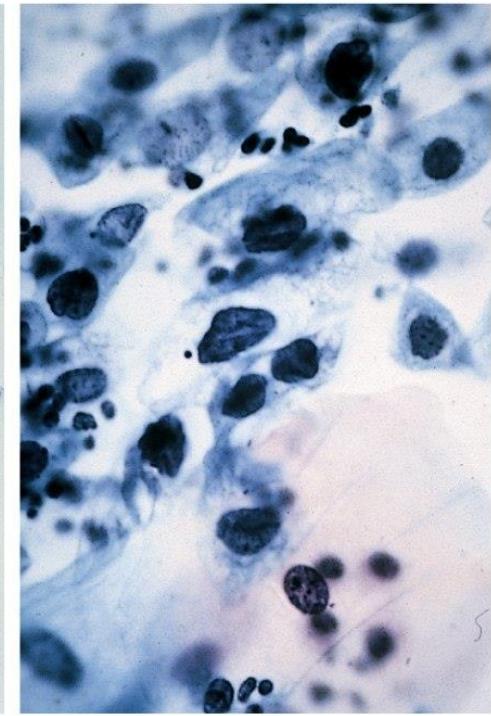


(A)

10 μm



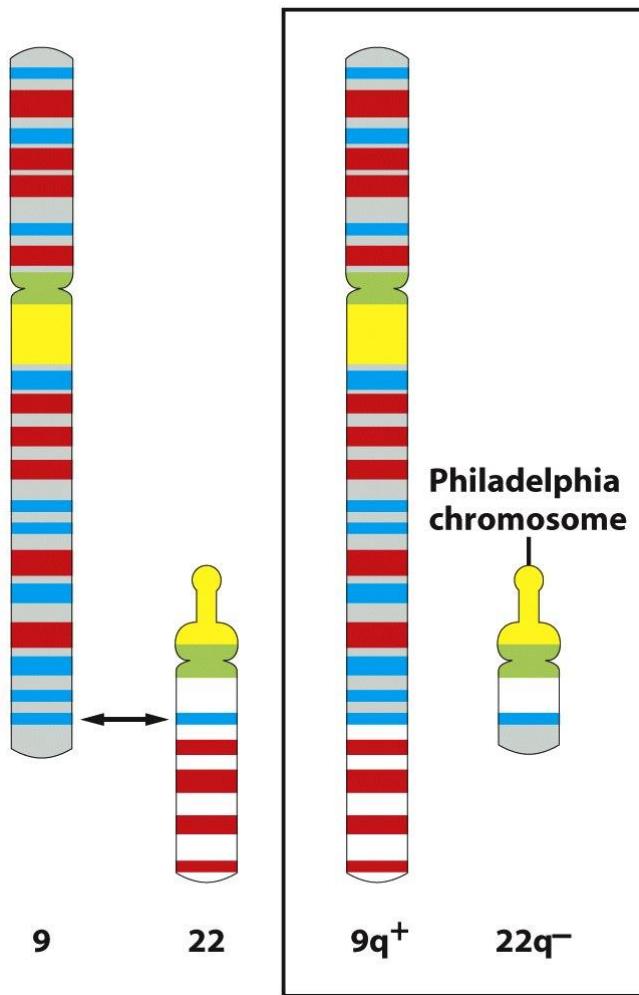
(B)



(C)

II. Features of cancer

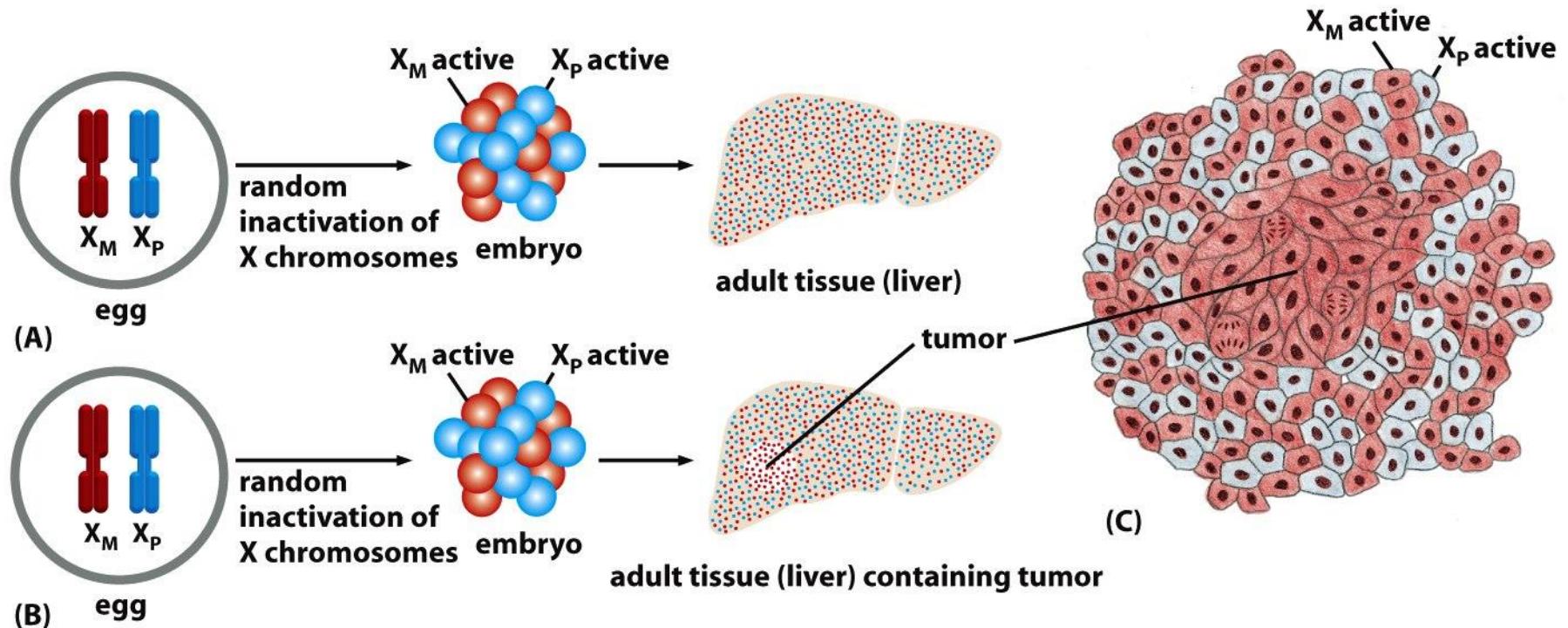
1. Monoclonal origin of cancer



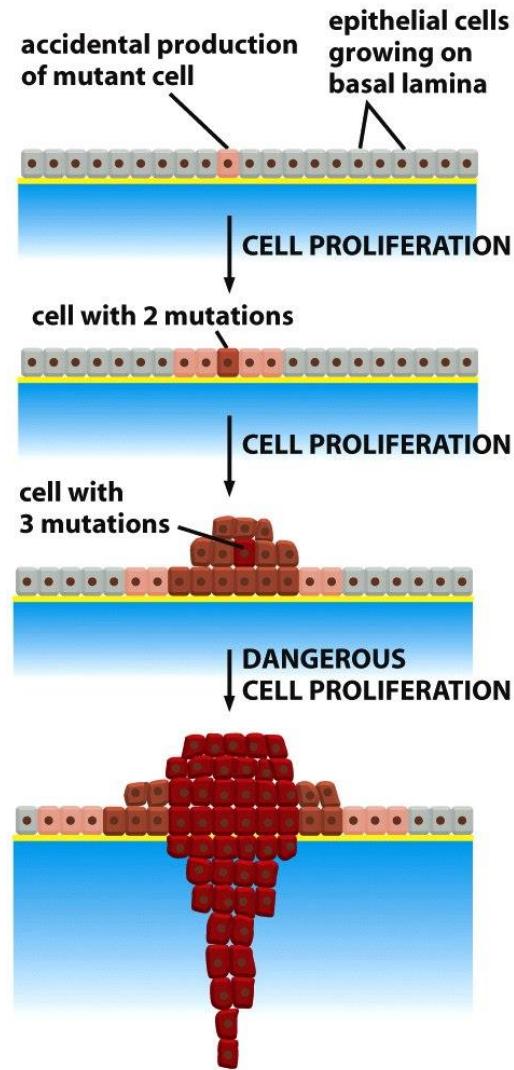
Chronic myelogenous leukemia

All cancer cells have the same translocation
Of chromosome

Evidence from X-inactivation mosaics that demonstrates the monoclonal origin of cancers



2. Somatic mutations in cancer



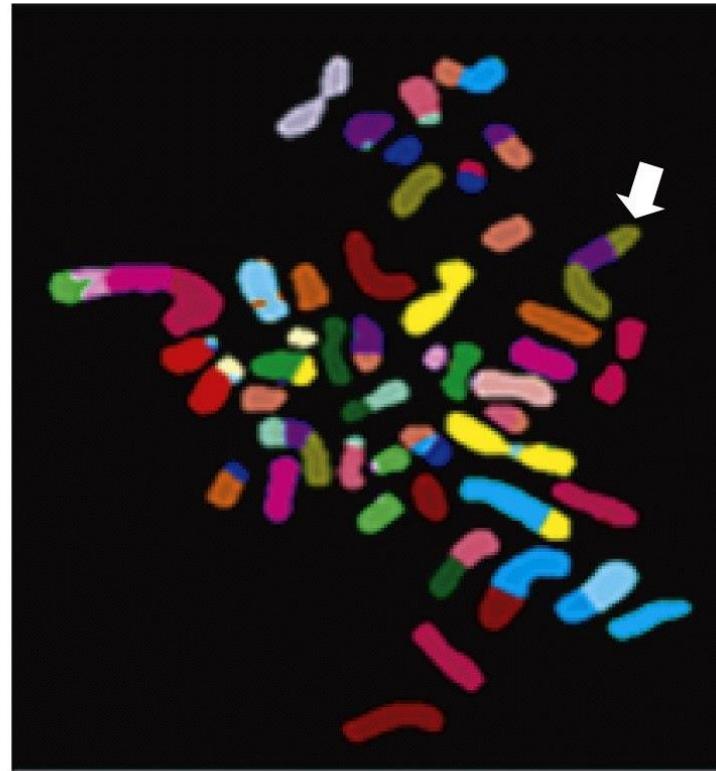
Usually multiple mutations
drive cancer initiation

3.Cancer genomes are highly unstable

- Polyploidy, aneuploidy, translocations, etc.

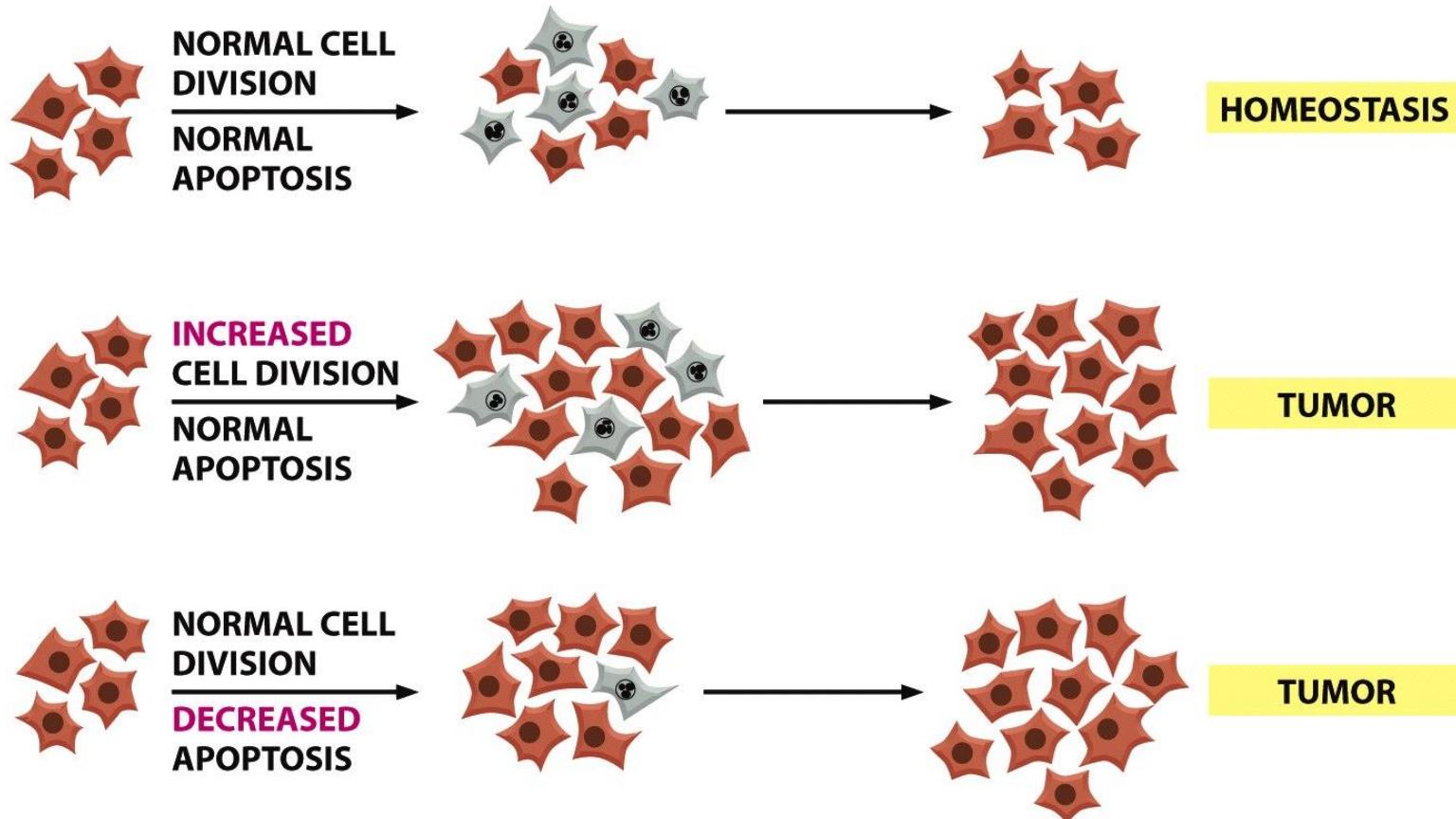


(A)



(B)

4. Escape normal restrictions on proliferation potential

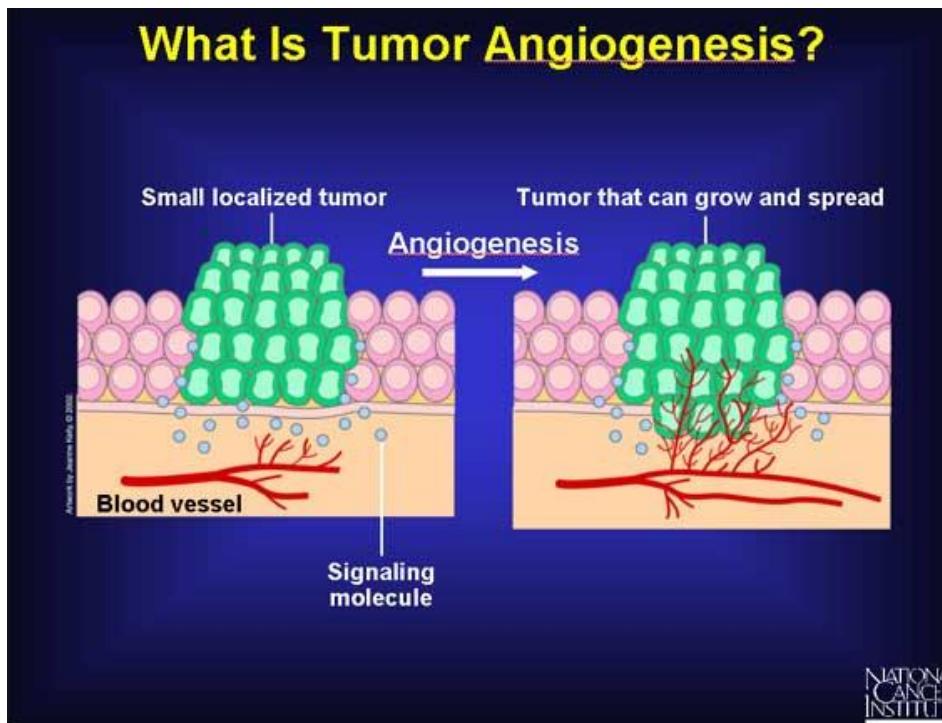


5. Abnormal response to DNA damage and other stresses

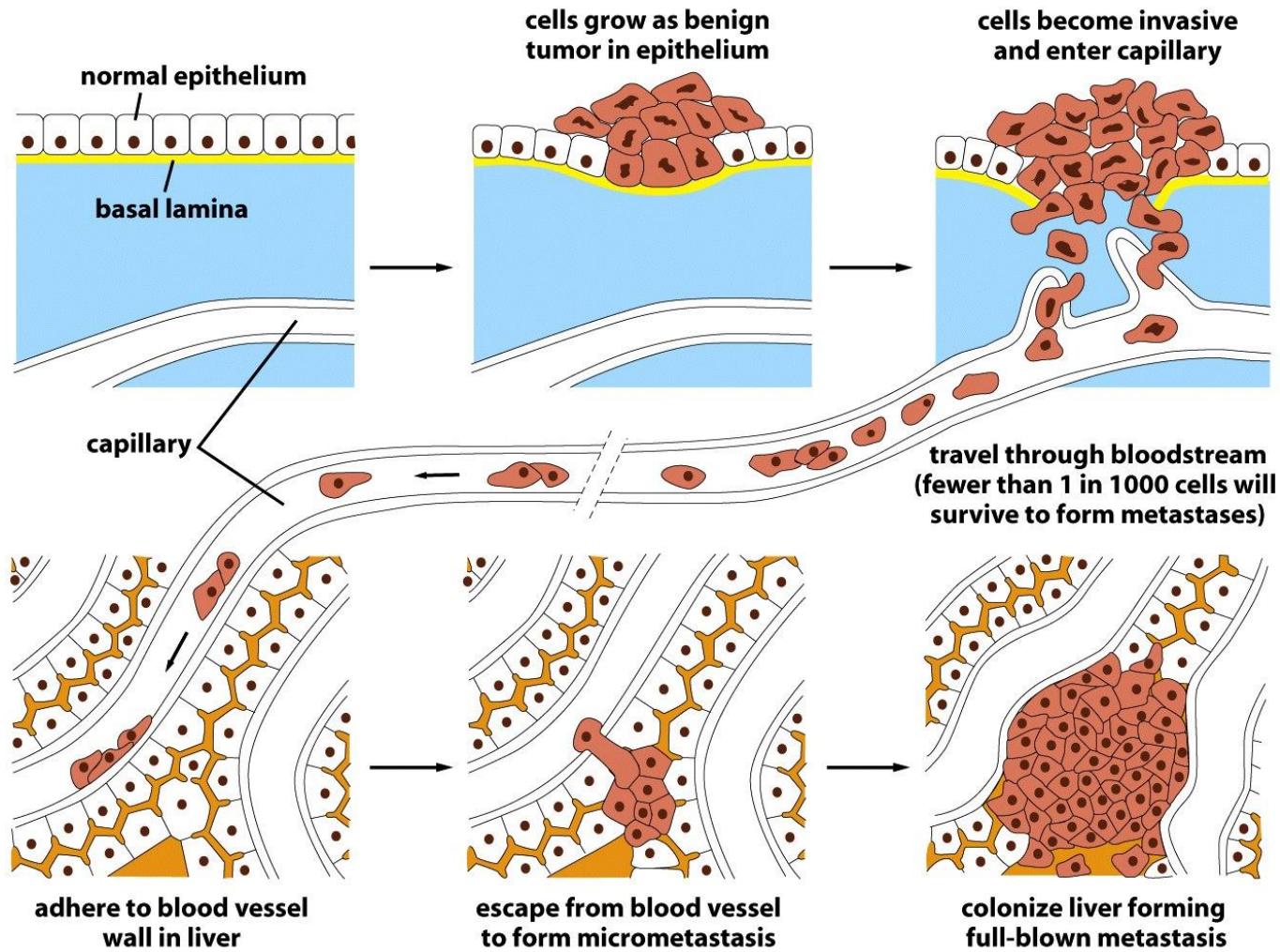
- A. **DNA damage:** p53 mutations, ATM mutations, failure to arrest cell cycle or cause apoptosis, producing more genetic mutations in each cell cycle.
- B. **Warburg effects:** increase glycolysis versus oxidative phosphorylation, tumor tends to ferment.
- C. **Growth factor –independent**
- D. **Failure to arrest cell cycle or apoptosis due to oncogene stress.**

6. High activity of angiogenesis

- High levels of VEGF, downstream of Hif1 (hypoxia inducible factor)



7. The fatal step--- metastasis



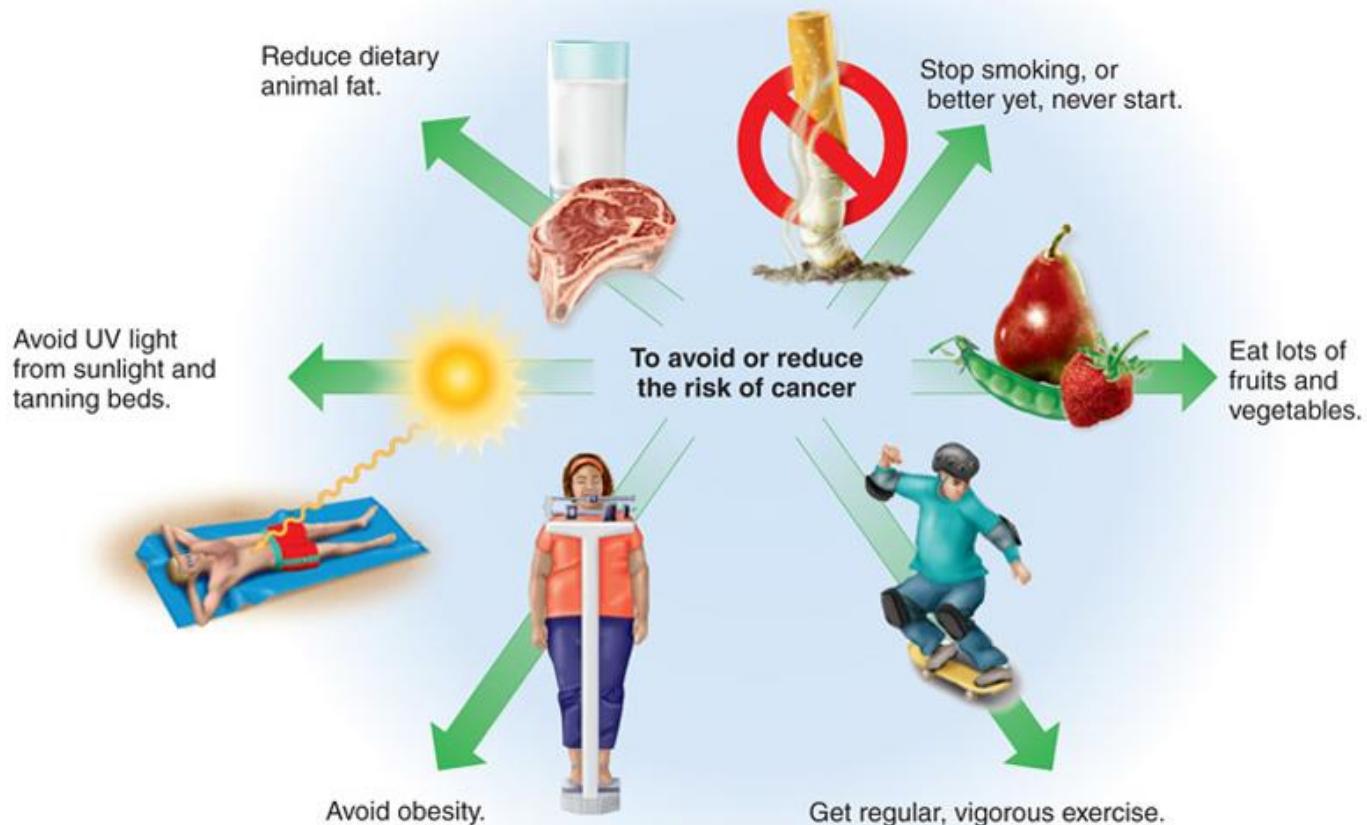
- Evading immune system attack ...

III. Cause of tumor

1. Life style
2. Environment
3. Carcinogen
4. Cancer causing virus

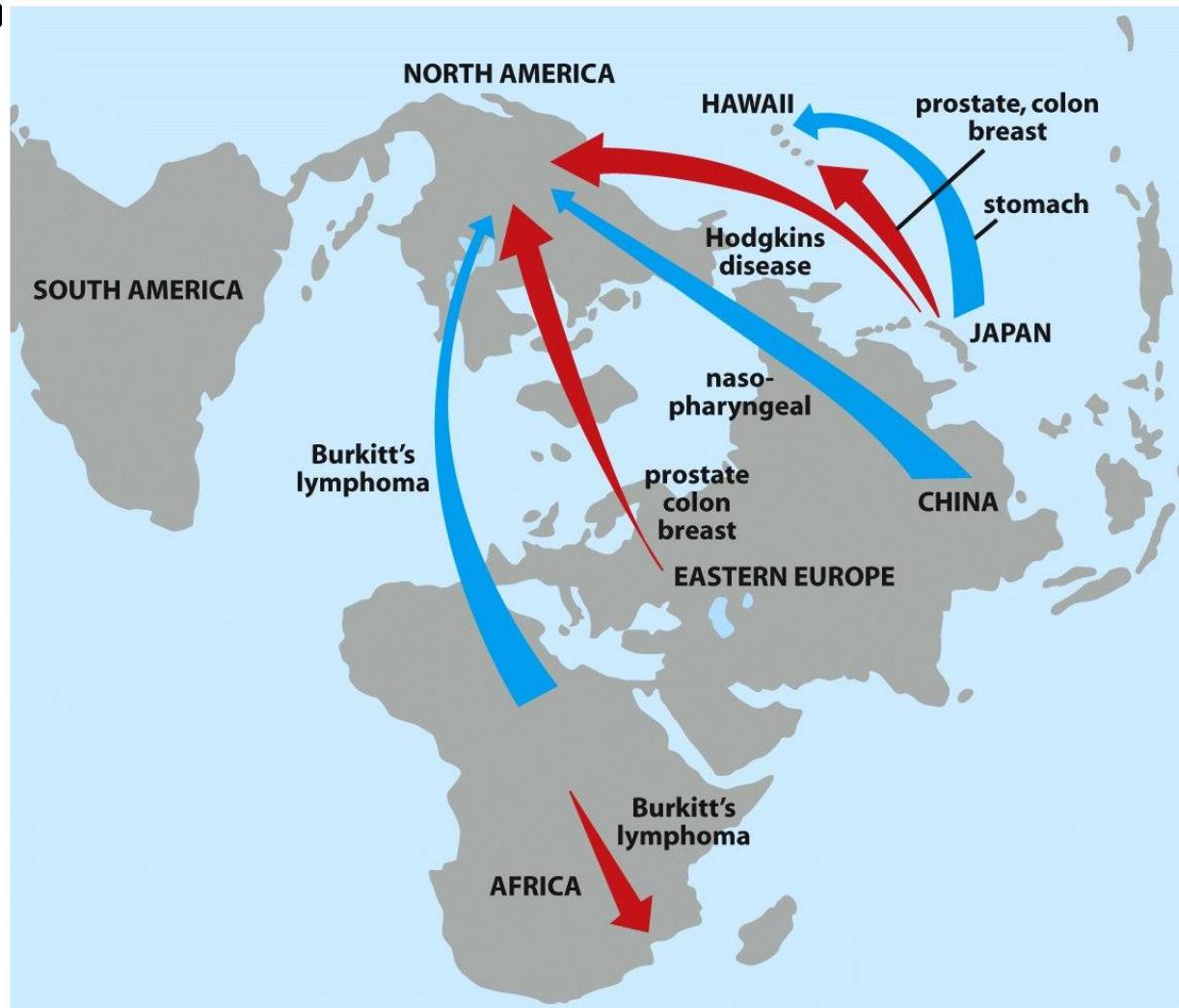
1. Life style

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2. Environment

- PM 2.5



- A summary about cancer types and environment and lifestyle factors

environmental and lifestyle factors	cancer	% total cases
• occupational exposure	various types	1–2
• tobacco related	lung, kidney, bladder	24
• diet: low in vegetables, high salt, high nitrate	stomach, esophagus	5
• diet: high fat, low fiber, fried and broiled foods	bowel, pancreas, prostate, breast	37
• tobacco and alcohol	mouth, throat	2

3. Carcinogen

- Broad sense: cancer causing agents, usually cause DNA damage.
Include: chemicals (aromatic compounds, nitrosamines, alkylating agent)
Irradiations, X-rays, UV, etc.

Some common chemical carcinogen

- Aflatoxin B1 (黃曲霉毒素)
 - Benzopyrene (苯丙芘)
 - Dimethylbenzanthracene (DMBA)
- } Converted by cytochrom c Oxidase into active carcinogen

- **VINYL CHLORIDE:**

liver angiosarcoma

- **BENZENE:**

acute leukemias

- **ARSENIC:**

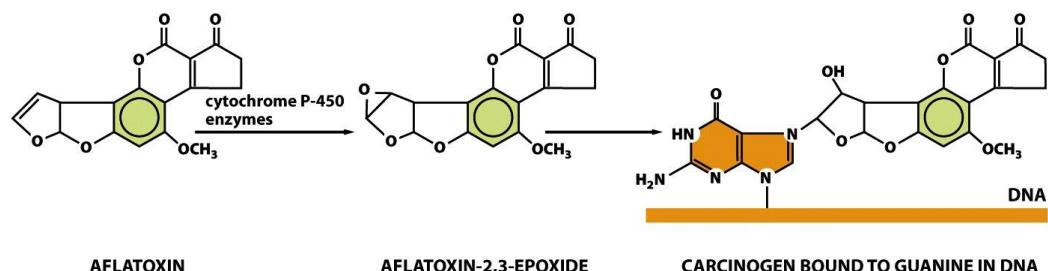
skin carcinomas, bladder cancer

- **ASBESTOS:**

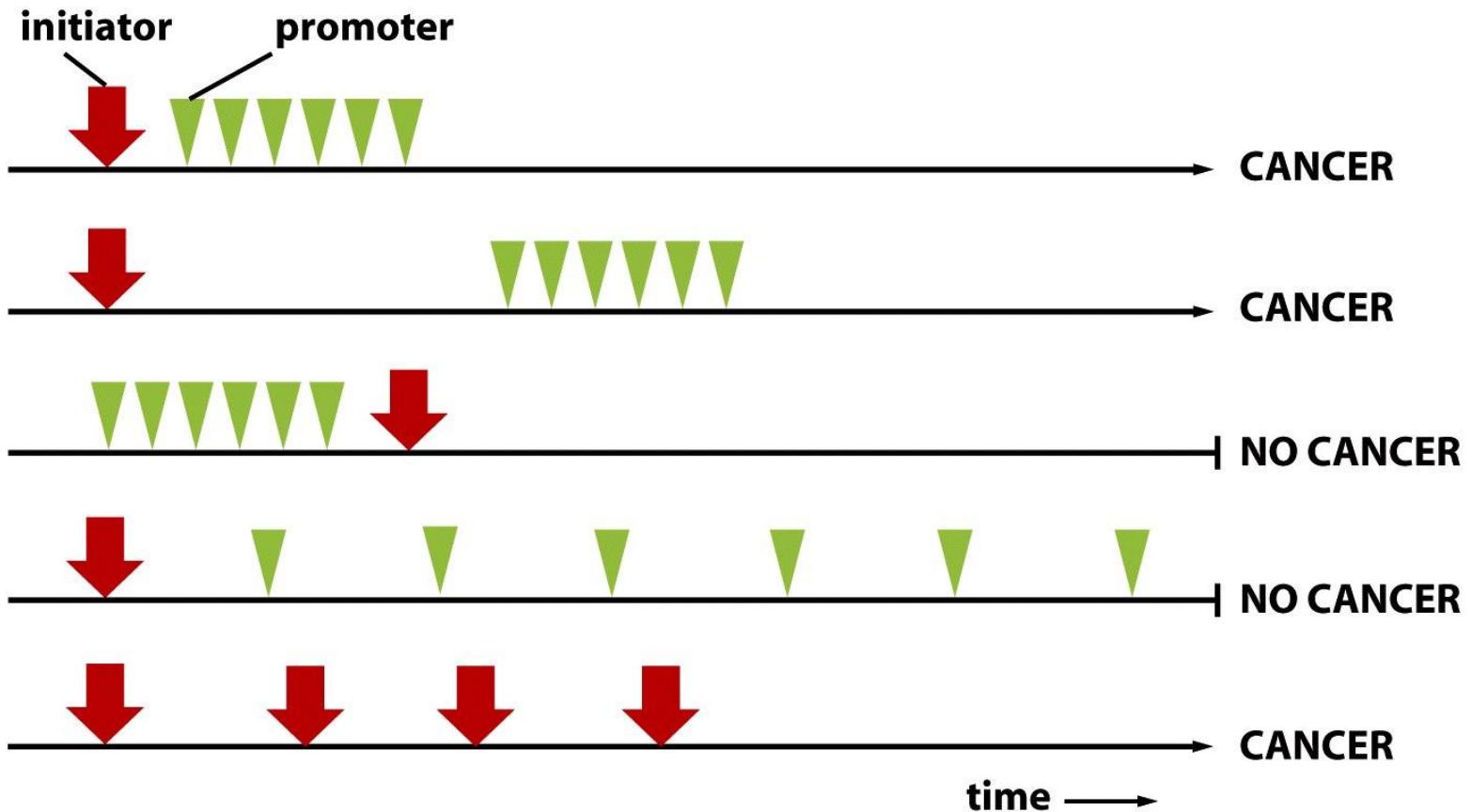
mesothelioma

- **RADIUM:**

osteosarcoma

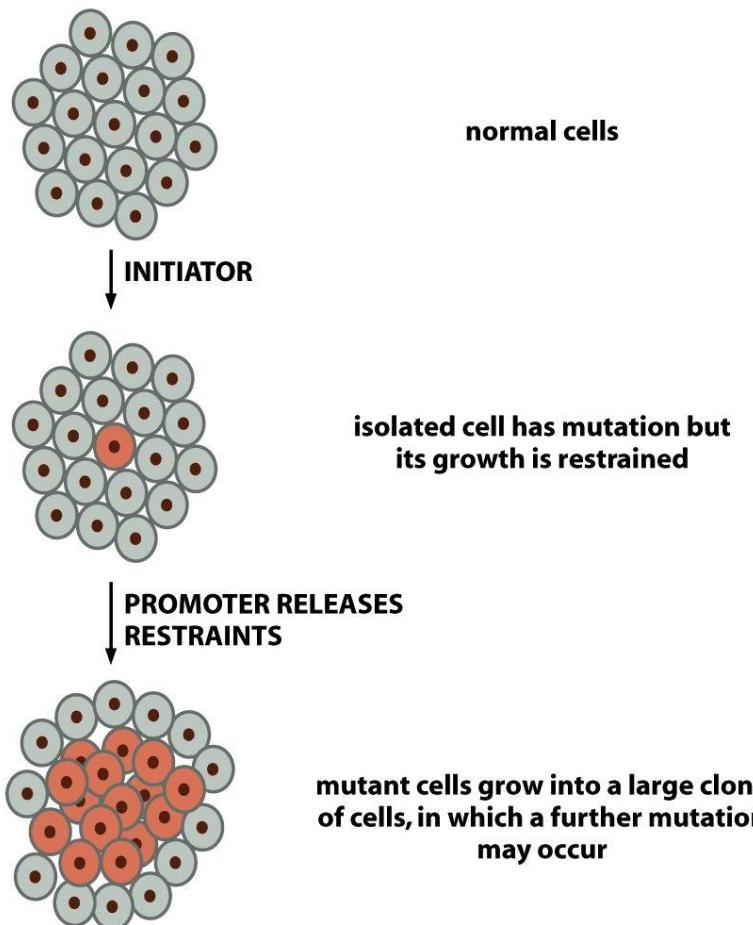


Difference between tumor initiator (mutagenic) and tumor promoter (non-mutagenic)



Functions for a tumor promoter

Example of tumor promoter: phorbol esters, which activates PKC kinase.



4. Cancer causing virus

Examples:

- HPV---vervical cancer
- MMTV-murine breast cancer
- HBV-liver cancer
- MMLV-leukemia,
- RSV- rat sarcoma
- Herpes virus-Burkitt's lymphoma , etc.

Table 20–1 Viruses Associated with Human Cancers

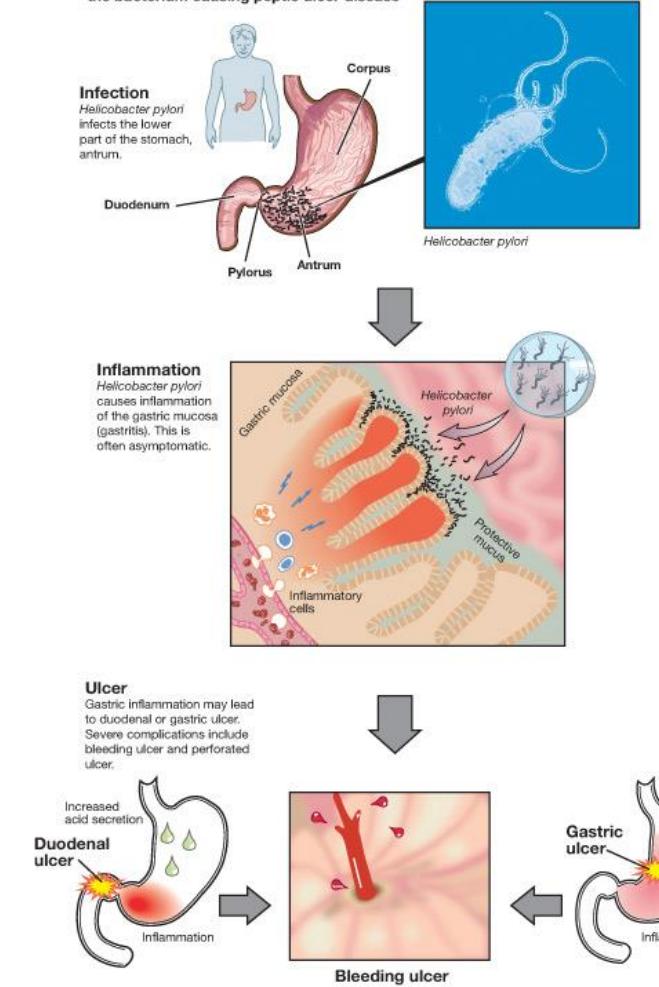
VIRUS	ASSOCIATED CANCER	AREAS OF HIGH INCIDENCE
DNA viruses		
Papovavirus family		
Papillomavirus (many distinct strains)	warts (benign) carcinoma of the uterine cervix	worldwide worldwide
Hepadnavirus family		
Hepatitis-B virus	liver cancer (hepatocellular carcinoma)	Southeast Asia, tropical Africa
Hepatitis-C virus	liver cancer (hepatocellular carcinoma)	worldwide
Herpesvirus family		
Epstein–Barr virus	Burkitt's lymphoma (cancer of B lymphocytes) nasopharyngeal carcinoma	West Africa, Papua New Guinea 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 immunodeficiency virus (HIV, the AIDS virus)	Kaposi's sarcoma	Central and Southern Africa

For all these viruses, the number of people infected is much larger than the numbers who develop cancer: the viruses must act in conjunction with other factors. Moreover, some of the viruses contribute to cancer only indirectly; HIV, for example, destroys helper T lymphocytes, which allows a herpes virus to transform endothelial cells. Similarly, hepatitis-C virus causes chronic hepatitis, which promotes the development of liver cancer.

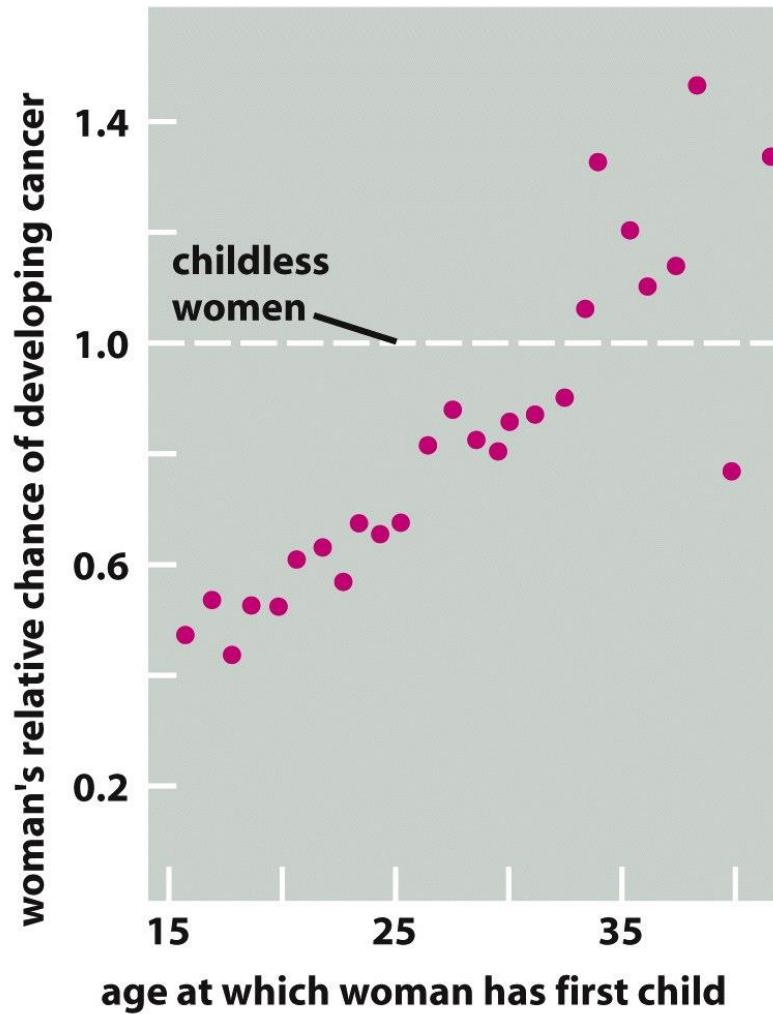
Helicobacter pylori---gastric cancer

Helicobacter pylori

— the bacterium causing peptic ulcer disease



Other factors

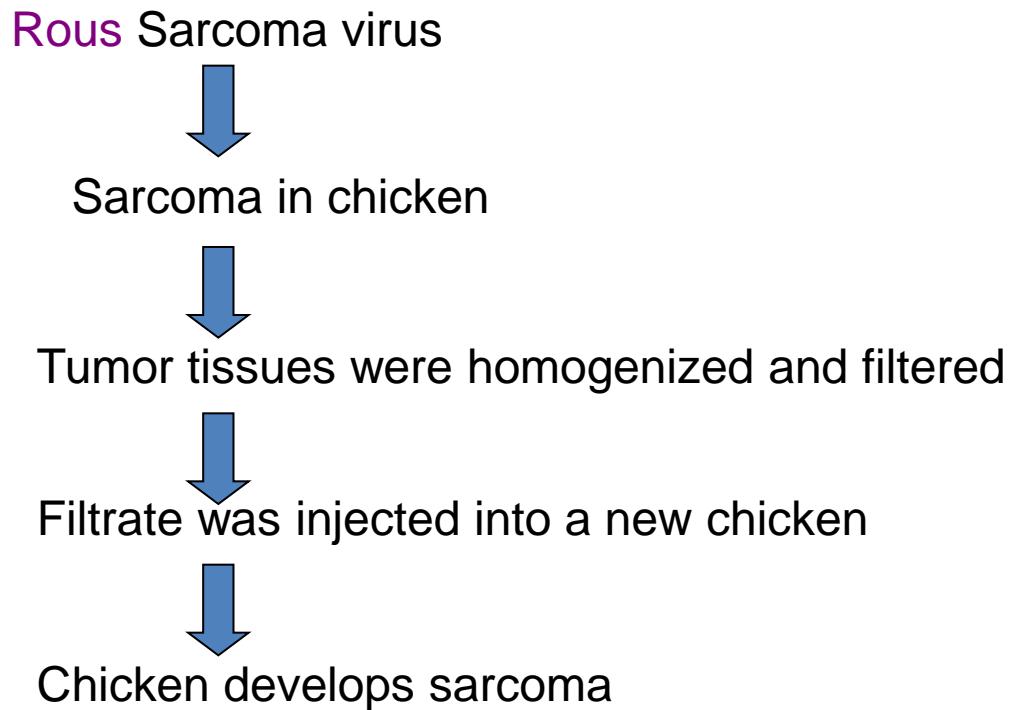


IV. Cancer critical genes

- 1. How were cancer critical genes discovered?
- 2. oncogene/proto-oncogene
- 3. tumor suppressor

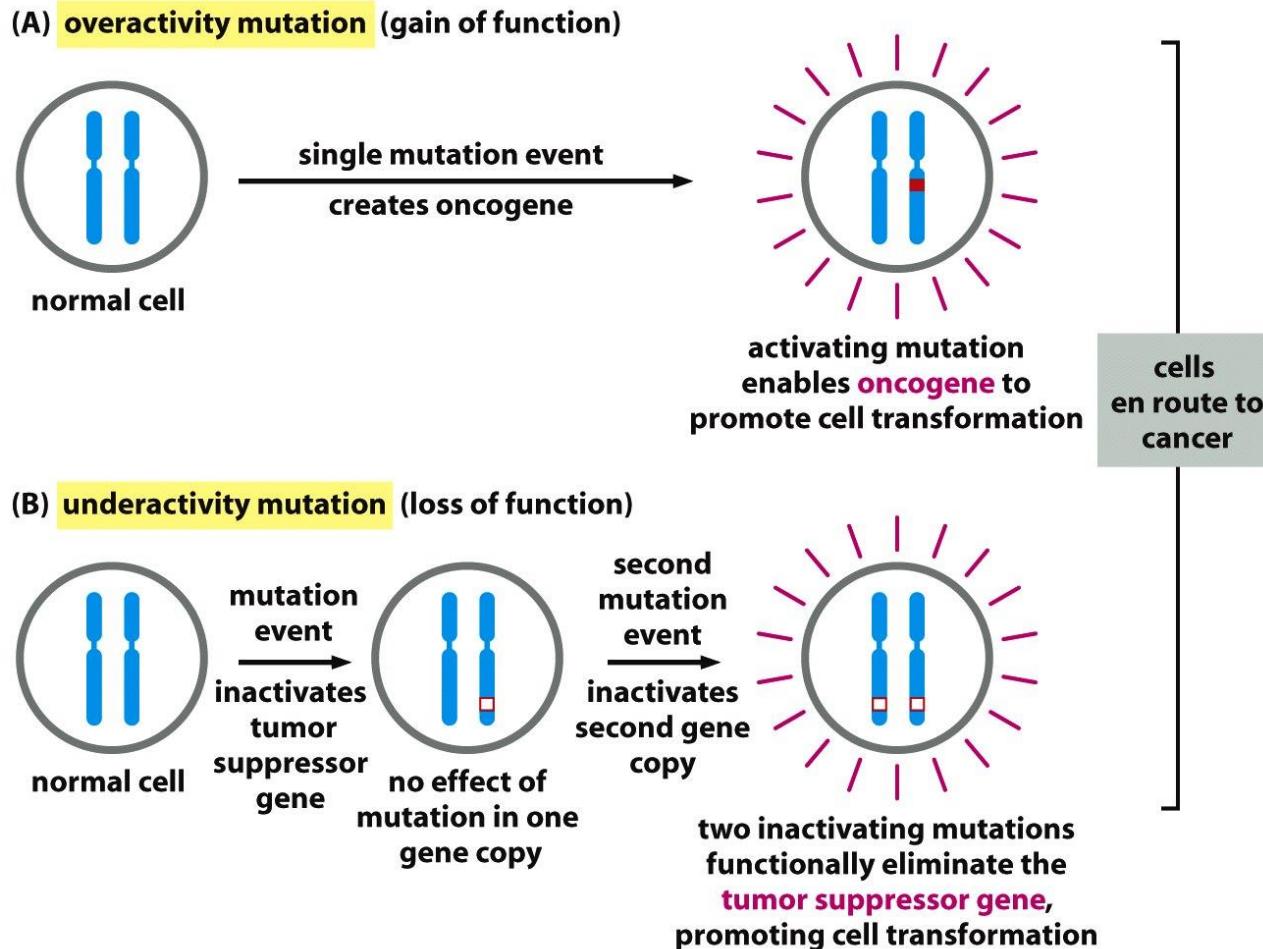
How were cancer critical genes discovered?

- Src discovery



Later found Rous sarcoma virus DNA can induce sarcoma formation

Oncogenes and tumor suppressors



Oncogenes/proto-oncogenes

- Gain of function of oncogenes leads to tumor formation
- Proto-oncogene normally does not trigger tumorigenesis, but its overactivation or overexpression leads to tumor formation

Tumor suppressors

Loss of function of tumor suppressors leads to tumor formation

Examples:

- Retinoblastoma
- P53
- ARF
- Tsc1
- Neurofibromin 1, etc.

Rb gene identification

- infected individual has a deletion of a certain band in his chromosome 13
- Both copy of Rb genes need to be defected to confer cancer phenotype

- Molecular mechanisms for cancer critical genes with examples

- Ras mutation in human cancers
 - Rb loss of heterozygosity
 - p53 mutation or loss
 - HPV
 - APC mutation in colon cancers

(1) Ras mutation

Table 4.2 A list of point-mutated *ras* oncogenes carried by a variety of human tumor cells

Tumor type	Proportion (%) of tumors carrying a point-mutated <i>ras</i> gene ^a
Pancreas	90 (K)
Thyroid (papillary)	60 (H, K, N)
Thyroid (follicular)	55 (H, K, N)
Colorectal	45 (K)
Seminoma	45 (K, N)
Myelodysplasia	40 (N, K)
Lung (non-small-cell)	35 (K)
Acute myelogenous leukemia	30 (N)
Liver	30 (N)
Melanoma	15 (N)
Bladder	10 (H, K)
Kidney	10 (H)

^aH, K, and N refer to the human *H-RAS*, *K-RAS*, and *N-RAS* genes, respectively.

Adapted from J. Downward, *Nature Rev. Cancer* 3:11–22, 2003.

Most oncogenic mutations on Ras occur on amino acid 12

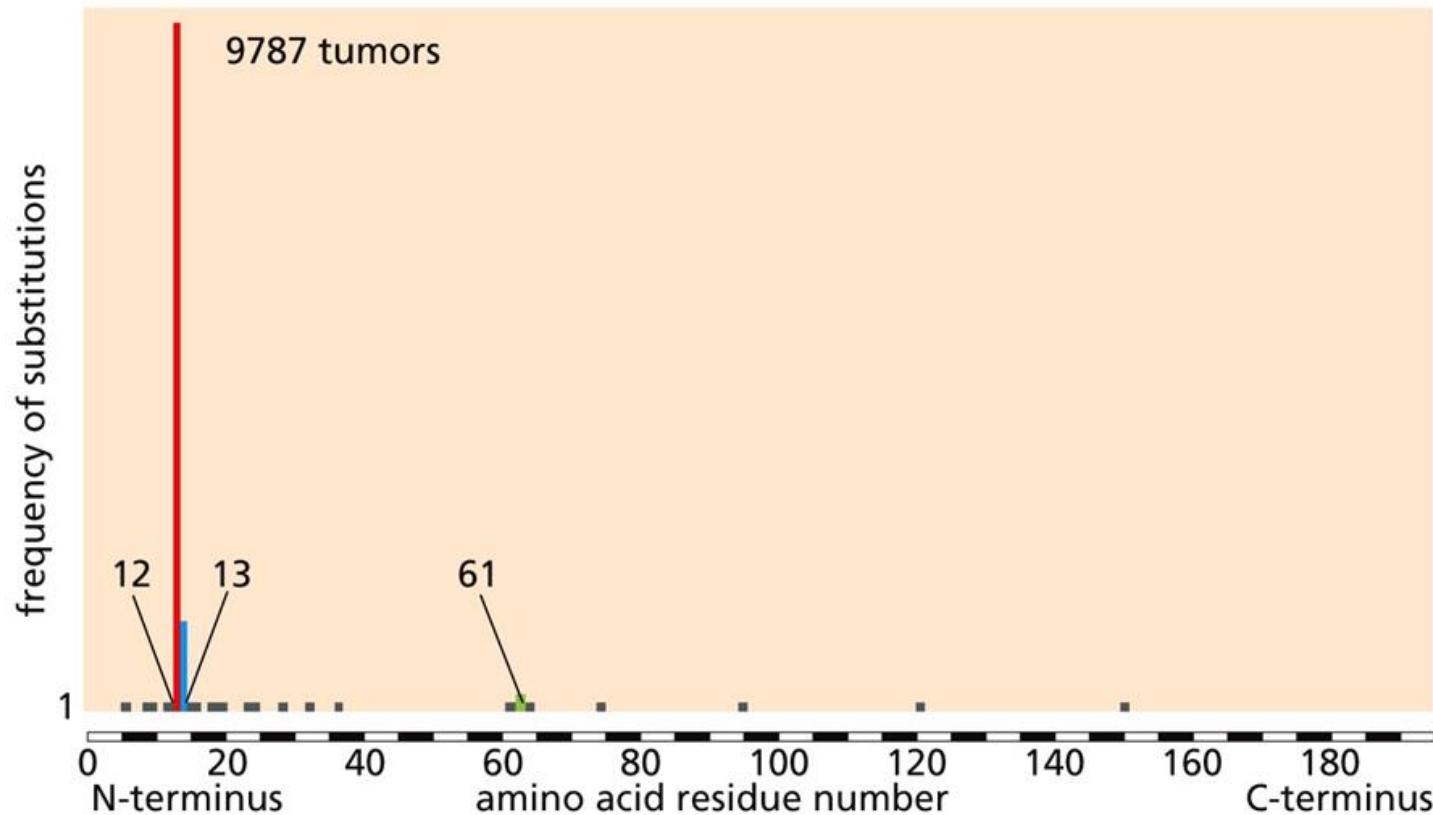


Figure 4.10 The Biology of Cancer (© Garland Science 2014)

(2) Rb loss of heterozygosity- (LOH) induces retinoblastoma

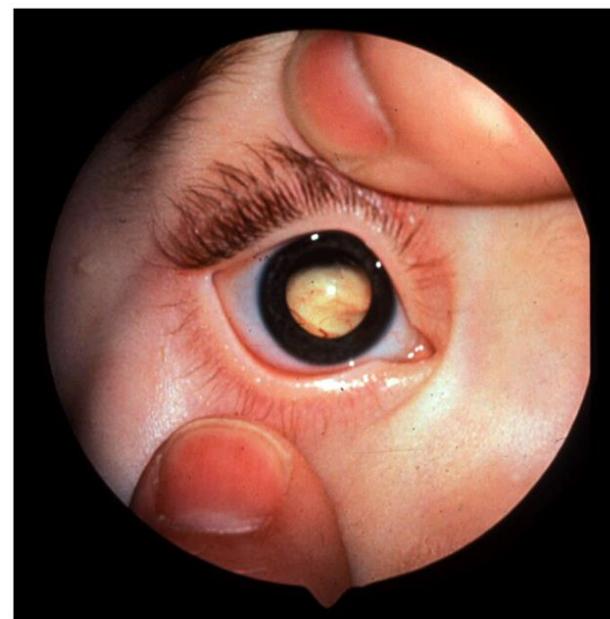
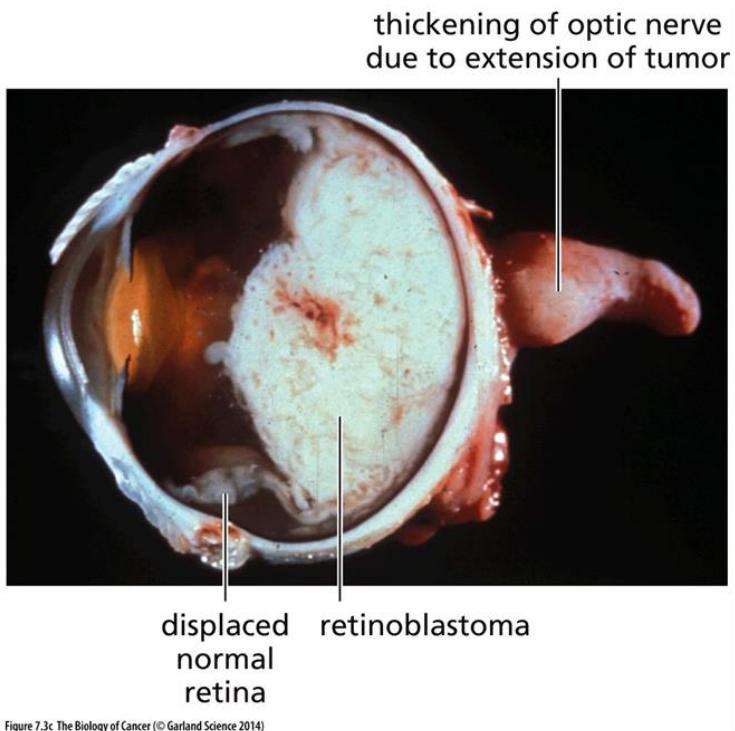


Figure 7.3d The Biology of Cancer (© Garland Science 2014)

Figure 7.3c The Biology of Cancer (© Garland Science 2014)

Rb and cell cycle control

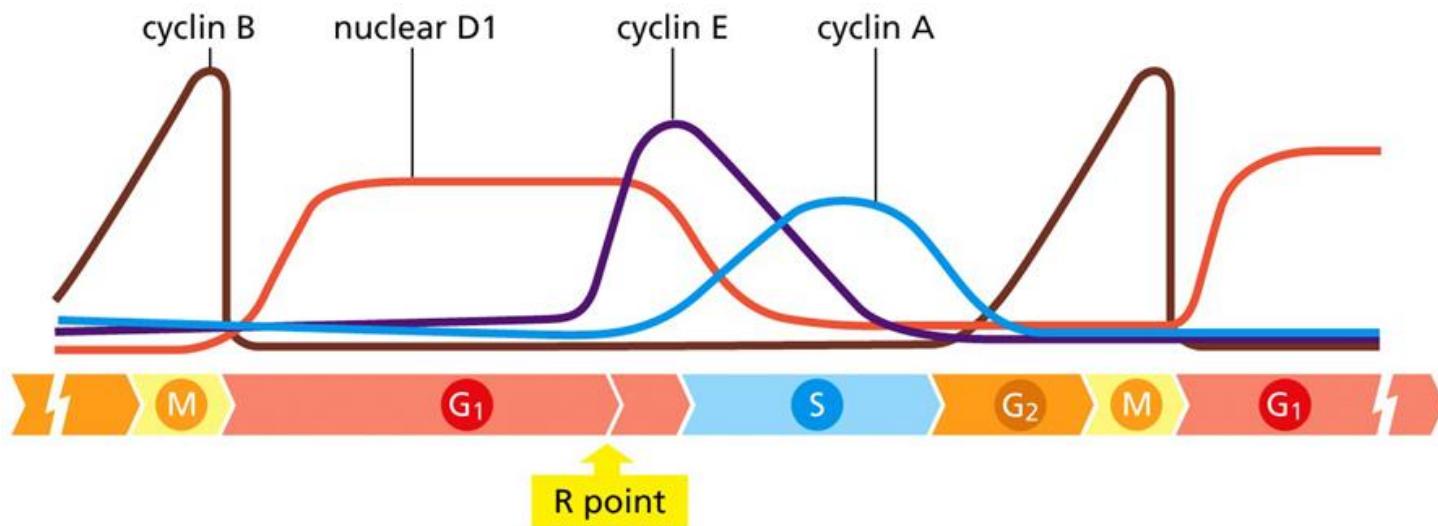


Figure 8.10 The Biology of Cancer (© Garland Science 2014)

Phosphorylation of Rb promotes cyclin E/cdk activity

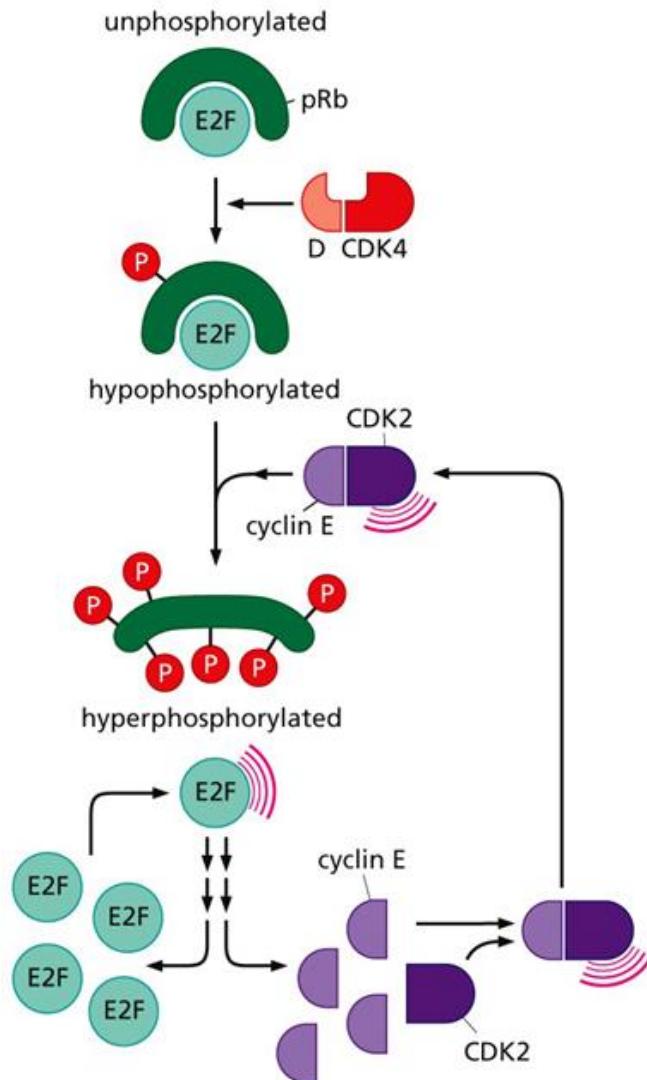


Figure 8.25a The Biology of Cancer (© Garland Science 2014)

Mutation of p53 in human cancers

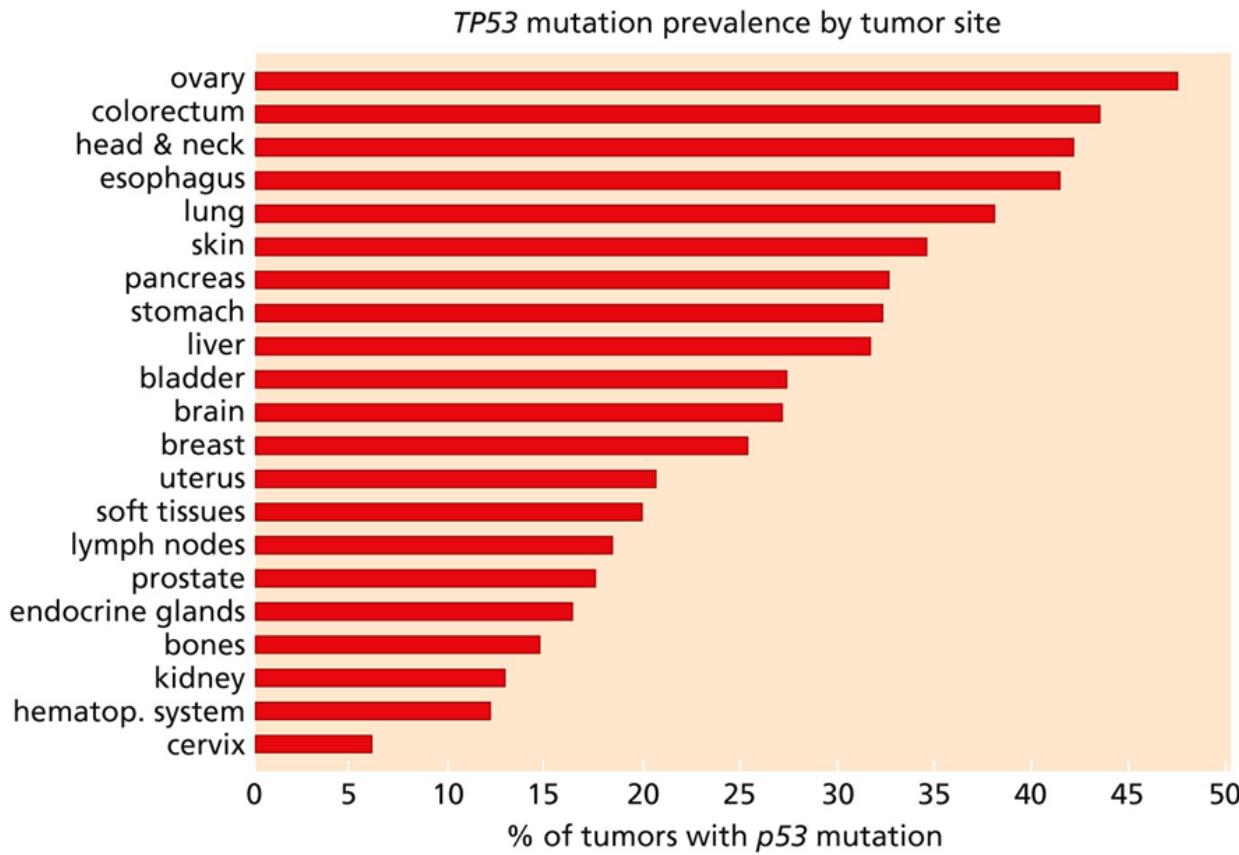


Figure 9.4 The Biology of Cancer (© Garland Science 2014)

Models of action of p53 tumor suppressor

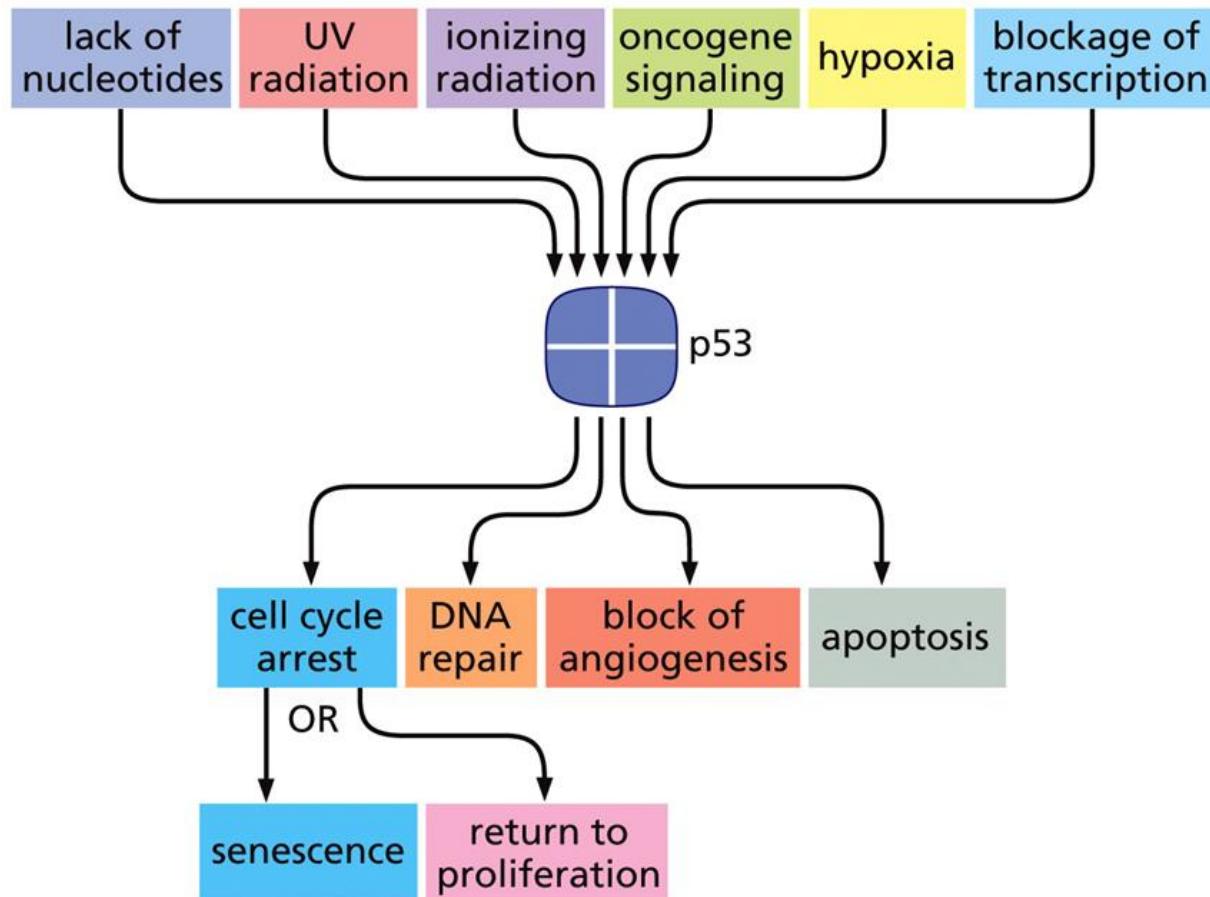
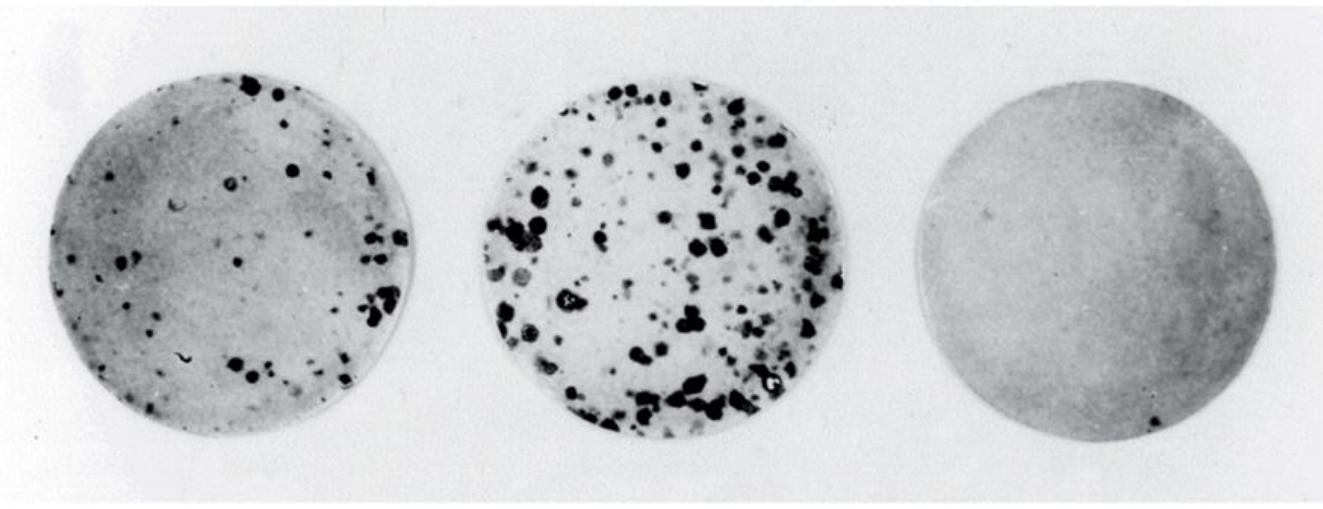


Figure 9.8 The Biology of Cancer (© Garland Science 2014)

Example



ras + p53
deletion mutant

ras + p53 val-135
point mutant

ras + p53
wild type

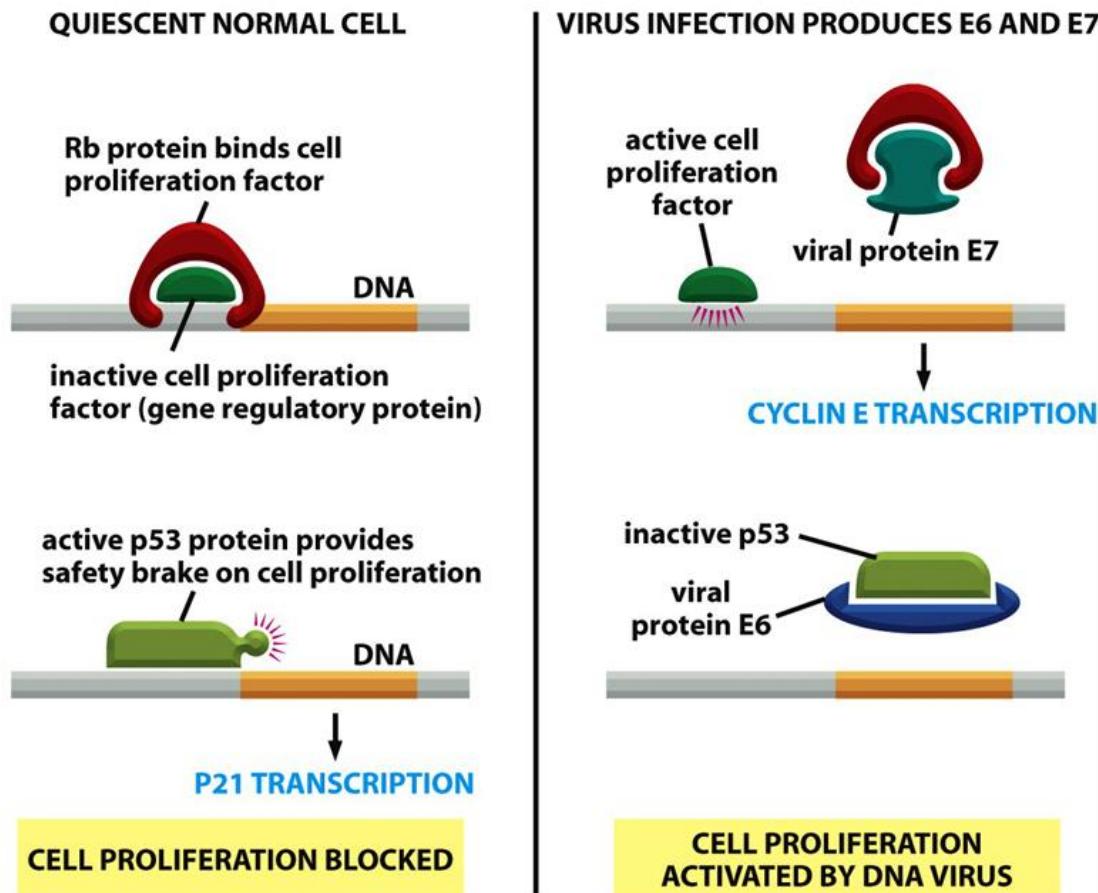
Figure 9.3 The Biology of Cancer (© Garland Science 2014)

p53 V135: gain of function



02.3_Visualization_of_Cancer_I_Lymphoma.wmv

Mode of action for HPV



APC mutation and human colon cancers

Table 20–2 Some Genetic Abnormalities Detected in Colorectal Cancer Cells

GENE	CLASS	PATHWAY AFFECTED	HUMAN COLON CANCERS (%)
<i>K-Ras</i>	oncogene	receptor tyrosine-kinase signaling	40
<i>β-catenin</i> ¹	oncogene	Wnt signaling	5–10
<i>Apc</i> ¹	tumor suppressor	Wnt signaling	> 80
<i>p53</i>	tumor suppressor	response to stress and DNA damage	60
<i>TGFβ receptor II</i> ²	tumor suppressor	TGFβ signaling	10
<i>Smad4</i> ²	tumor suppressor	TGFβ signaling	30
<i>MLH1</i> and other DNA mismatch repair genes	tumor suppressor (genetic stability)	DNA mismatch repair	15 (often silenced by methylation)

The genes with the same superscript act in the same pathway, and therefore only one of the components is mutated in an individual cancer.

- APC LOH induces polyposis, which usually happens before colon cancer



Normal colon

(A)



Adenomatous polyposis

(B)

V. Multi-step tumorigenesis

Cancer take many years to develop

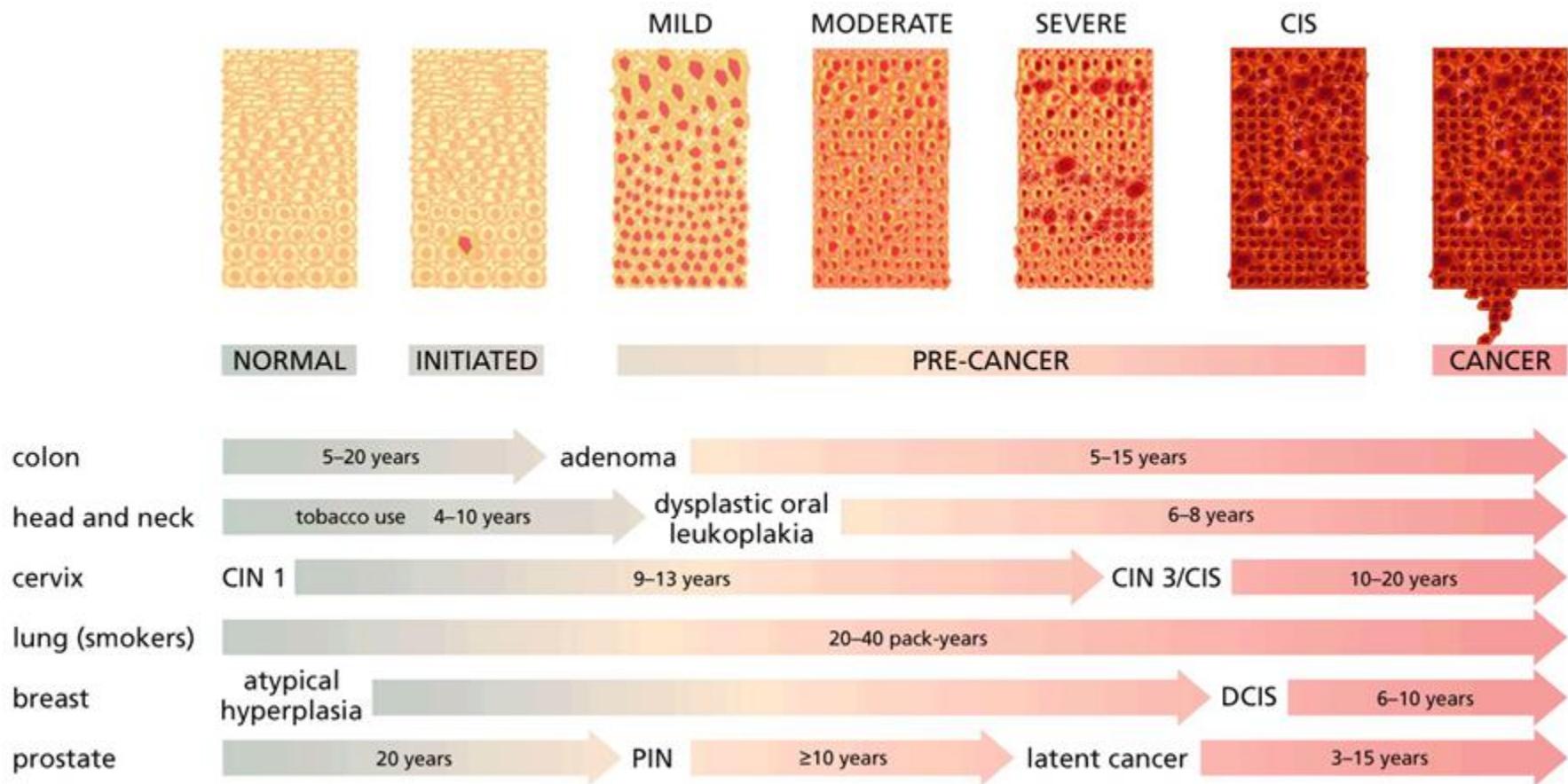


Figure 11.8a The Biology of Cancer (© Garland Science 2014)

Darwinian evolution and clonal succession

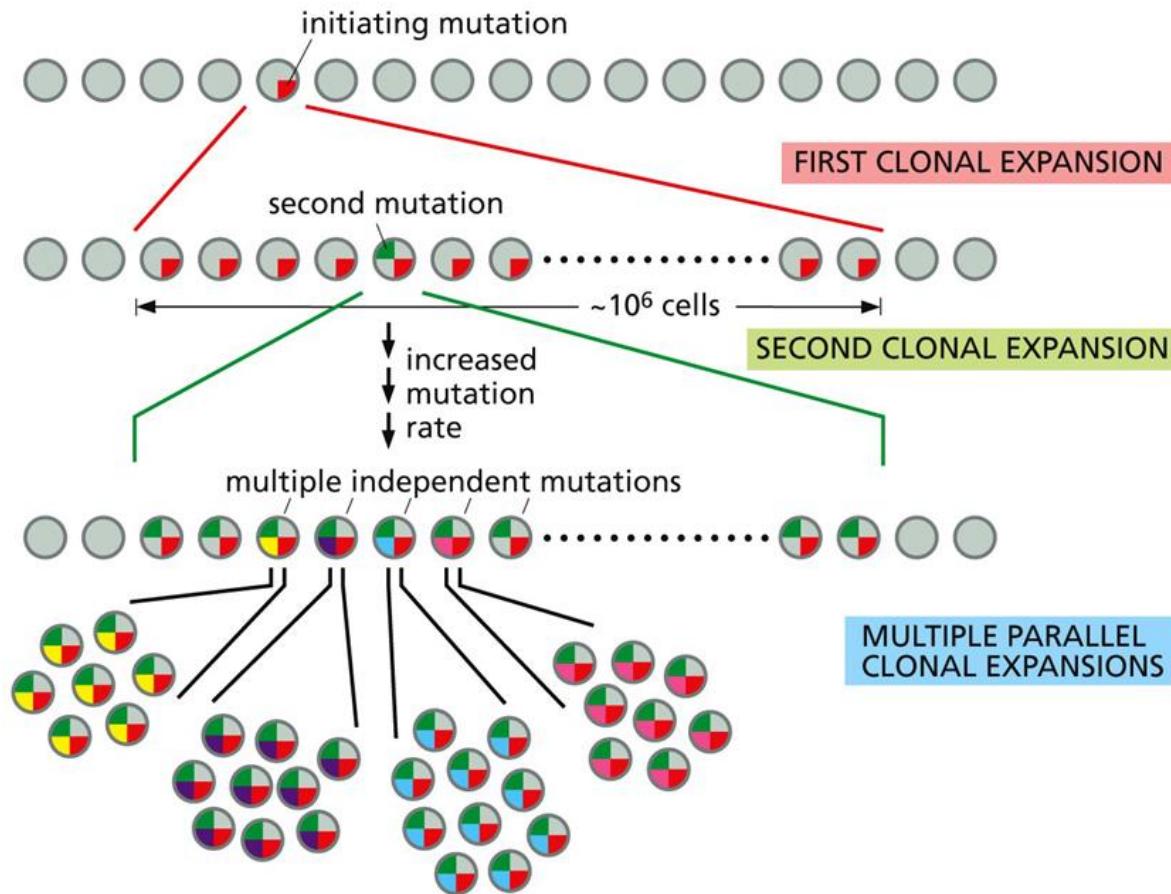
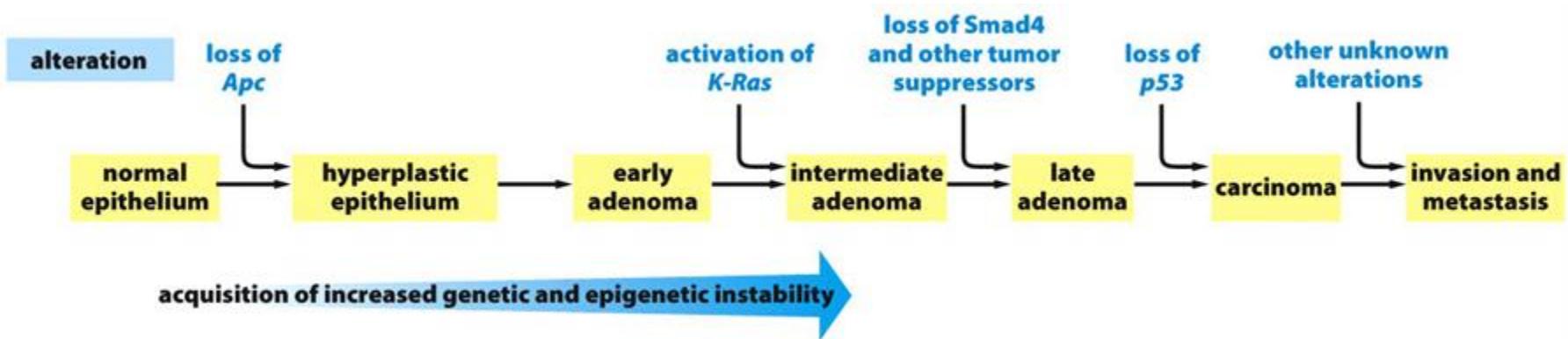


Figure 11.20a The Biology of Cancer (© Garland Science 2014)

- Genetic changes underlying the development of colorectal carcinoma



Diversification within a tumor

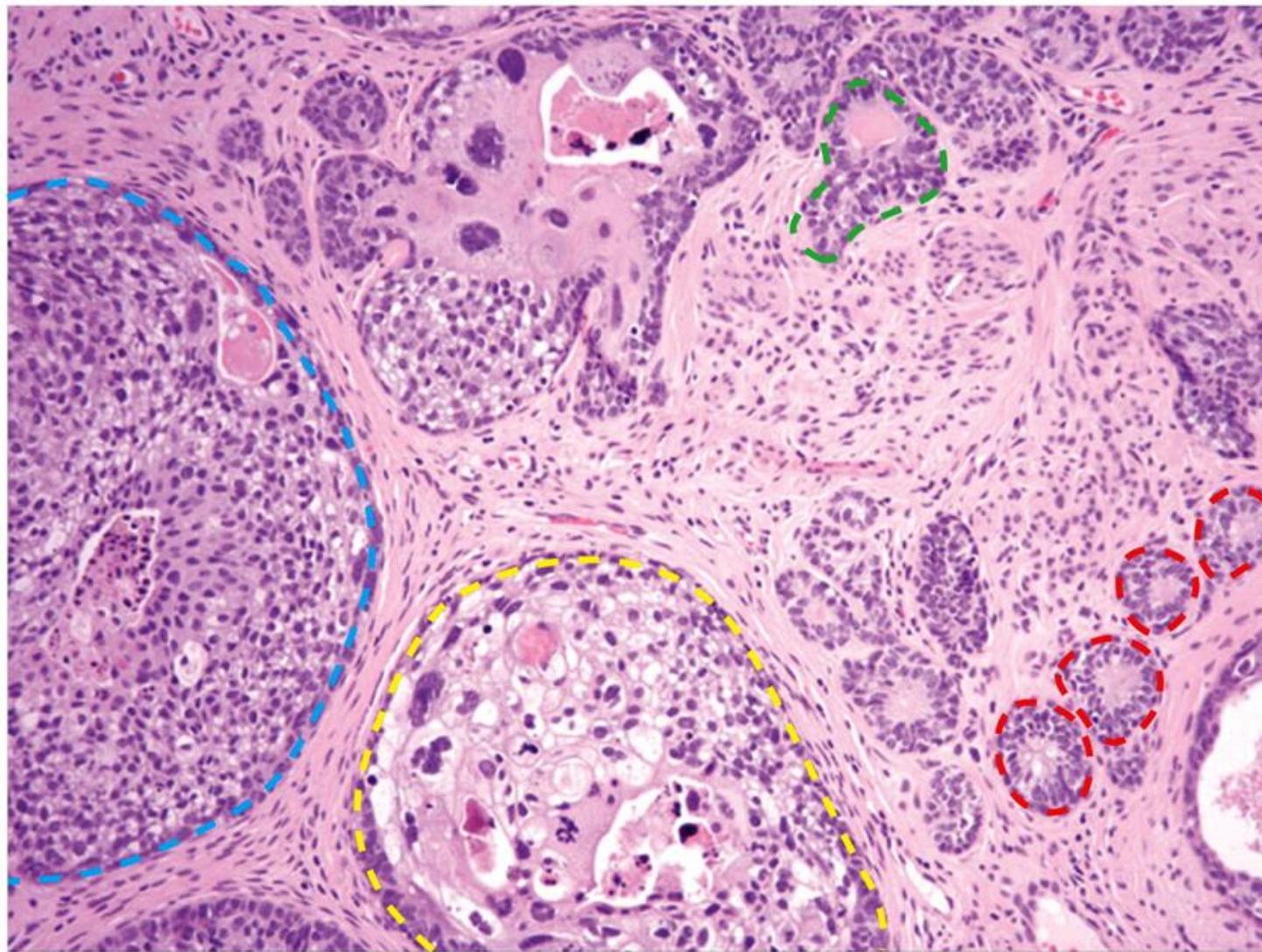


Figure 11.21a The Biology of Cancer (© Garland Science 2014)

VI. Cancer stem cells

Take a tumor mass, make single cell suspension



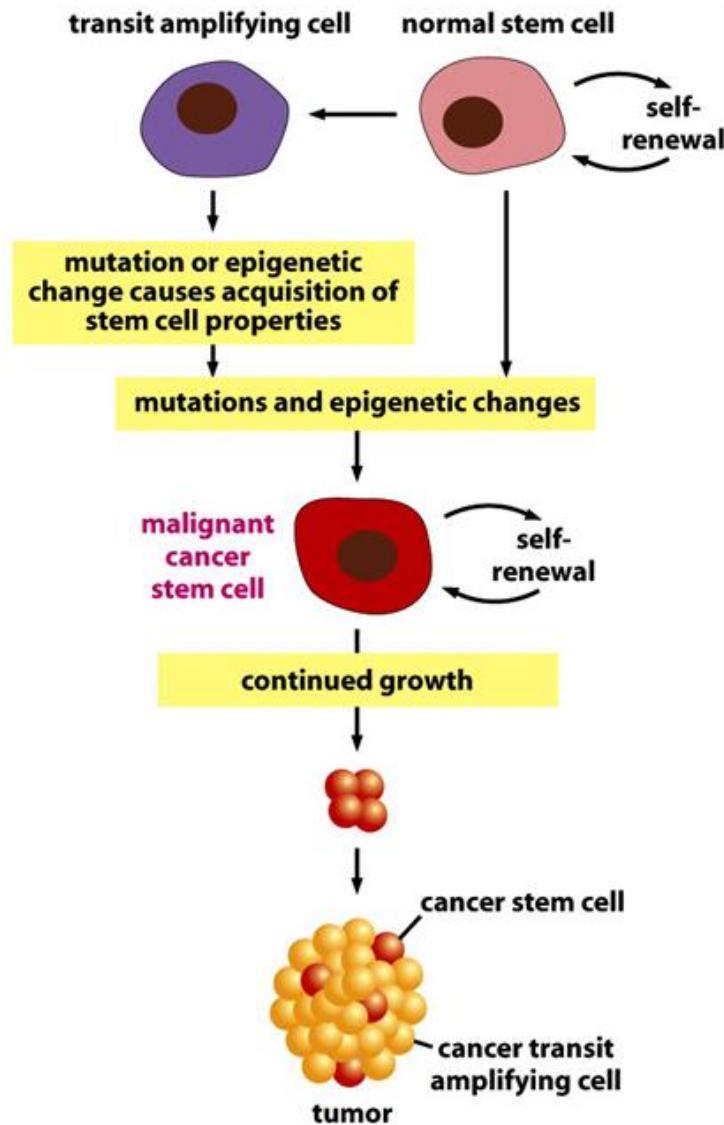
Inject single cell into immunodeficiency mice to induce tumor formation



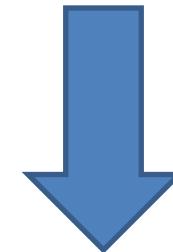
<<1% of the isolated cancer cells can induce a new tumor formation

Those that can induce tumor formation has the characteristics of **cancer stem cells**: They are capable of indefinite self-renewal, but they also give rise to rapidly cells that have limited capacity to self-renewal. They are responsible for maintaining the Population of cells in a tumor.

Cancers **may** arise from cancer stem cells



Tumor early stage
Differentiated cells



Tumor late stage
Poorly differentiated cells

VII. Tumor metastasis

Overview of metastasis---causing 90% of all cancer death

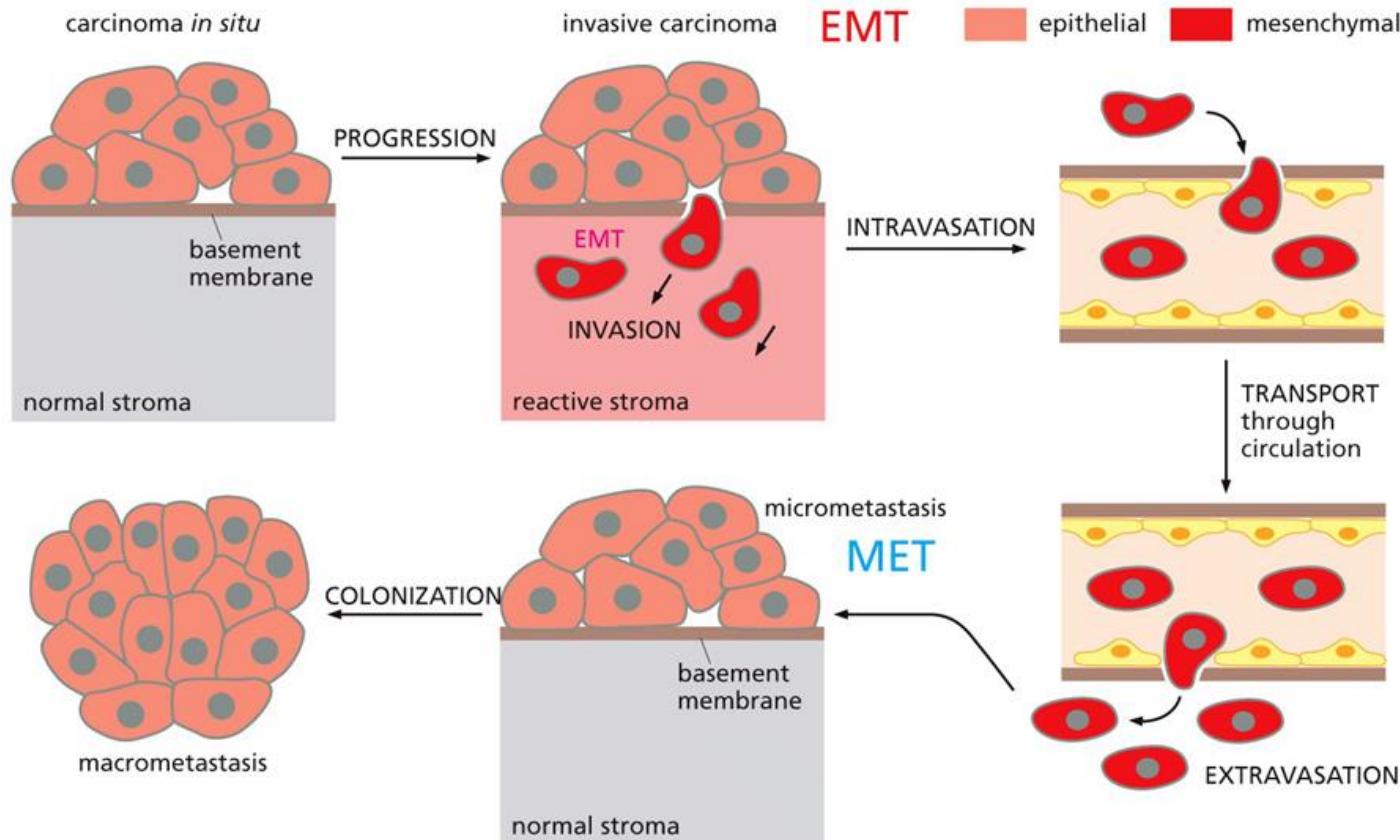


Figure 14.18b The Biology of Cancer (© Garland Science 2014)

- Epithelial-mesenchymal transition is important in metastasis

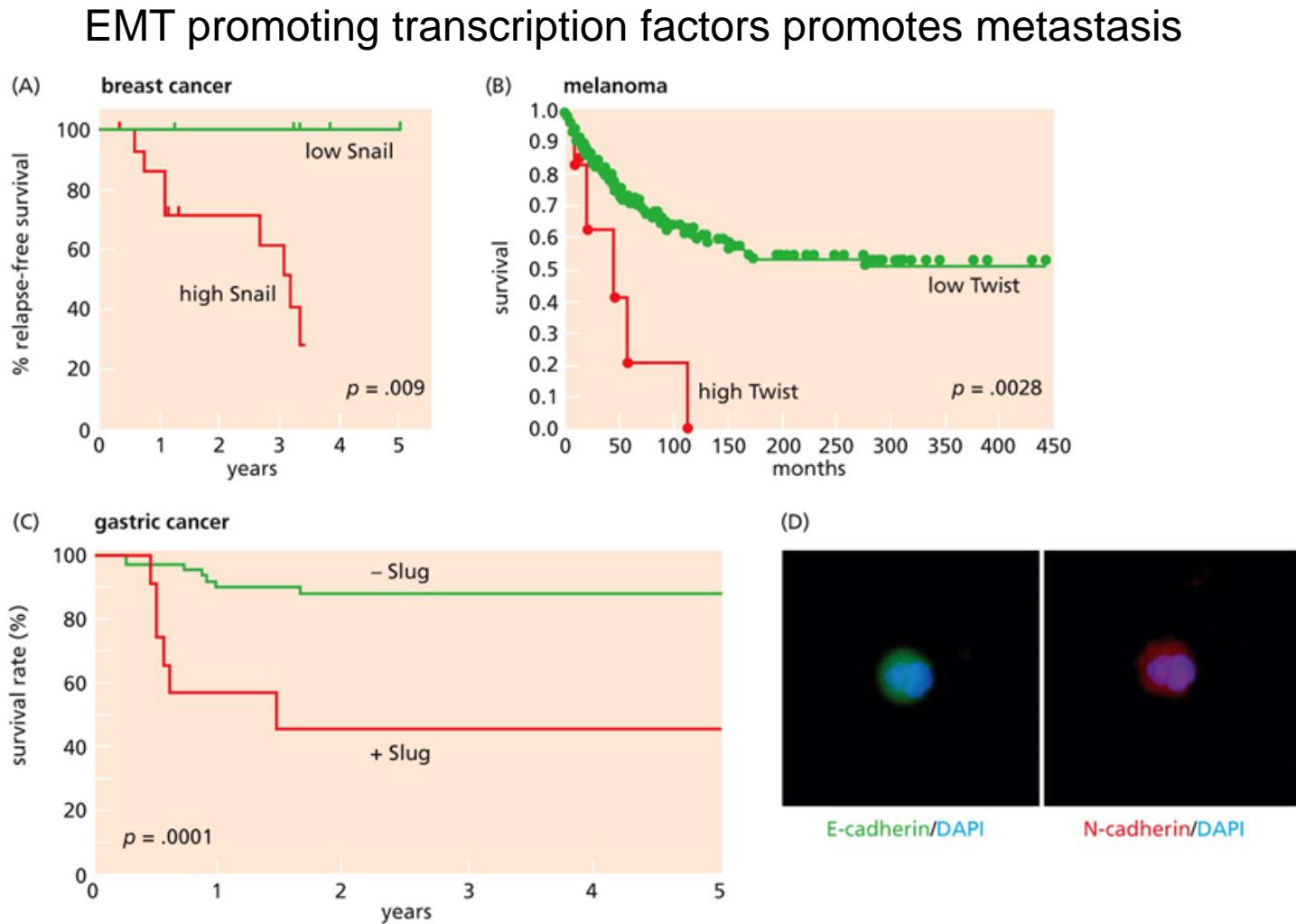


Figure 14.31 The Biology of Cancer (© Garland Science 2014)

EMT is associating to increased migration of epithelial cells

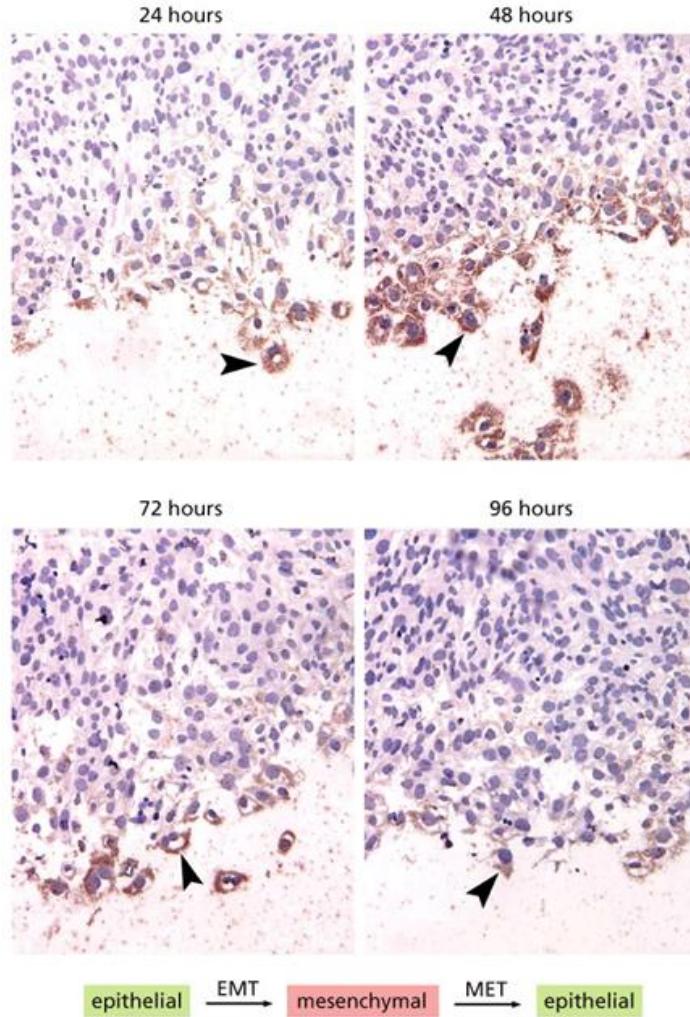


Figure 14.26 The Biology of Cancer (© Garland Science 2014)

Increased activity of MT-MMP, and many factors promote cancer invasion

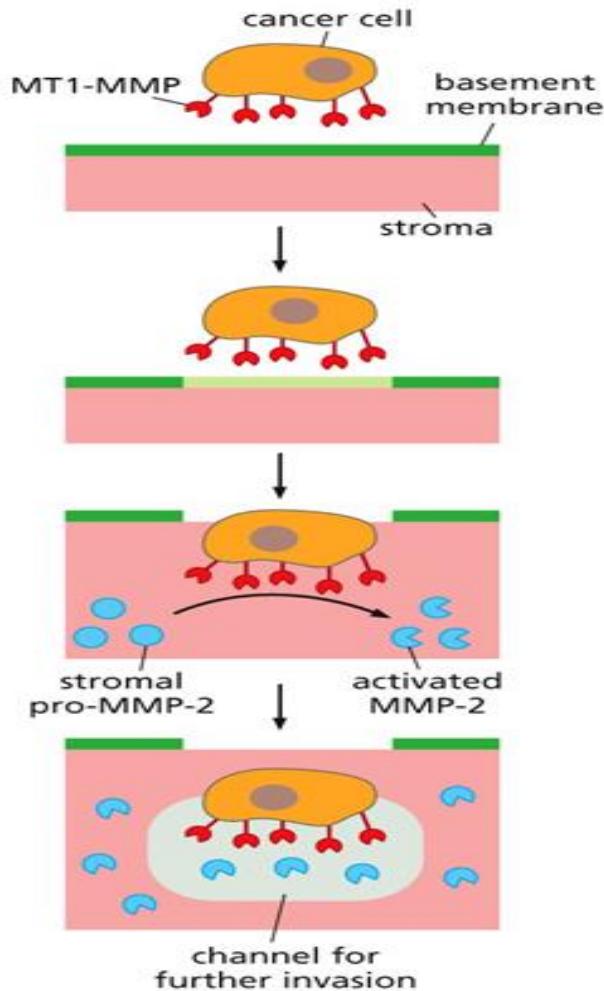


Figure 14.34 The Biology of Cancer (© Garland Science 2014)

VIII. Tumor treatment

- Traditional cancer treatment (before 1975)
 - Surgery
 - Chemotherapy
 - Radiotherapy

still take a major part
in cancer therapy
- Present and future in cancer treatment

Mortality rates for cancers in the past decades

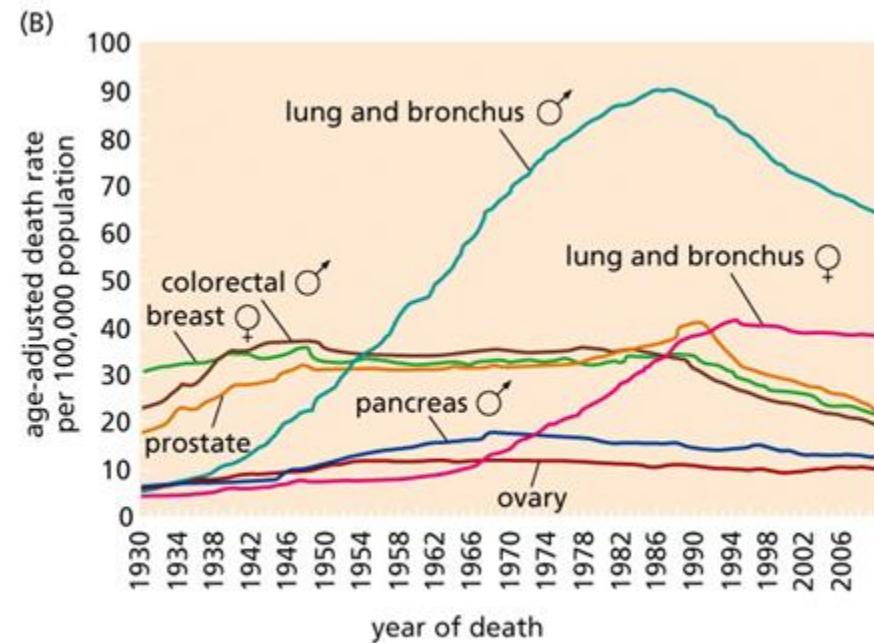
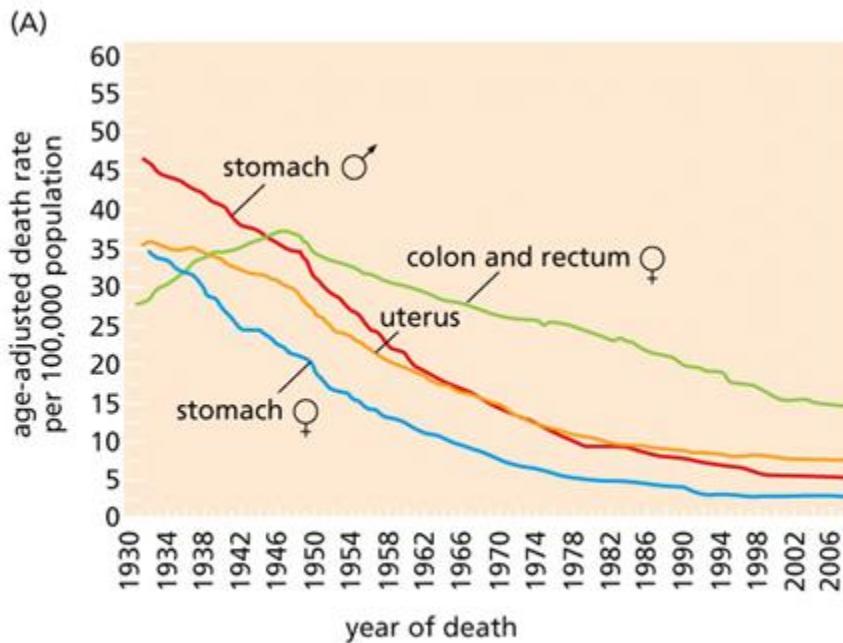


Figure 16.1 The Biology of Cancer (© Garland Science 2014)

improved food storage, awareness in Helicobacter pylori
early detection and surgery increase survival rates for
Certain types of cancer

Chemotherapy drugs

Examples for some of them, all are generally cytotoxic:

Table 16.2 Examples of antimetabolites used to treat cancer

Name	Chemical structure	Targeted reaction	Examples of clinical use
methotrexate	folate analog	formation of tetrahydrofolate	breast cancer, lymphomas
6-mercaptopurine	purine analog	purine biosynthesis	leukemia, NHL
doxorubicin	natural product ^a	intercalating agent, inhibits topoisomerase	wide range
thioguanine	guanine analog	purine biosynthesis	acute granulocytic leukemia
fludarabine	purine analog	ribonucleotide reductase, DNA replication	chronic lymphocytic leukemia, NHL
cladribine	adenosine analog	adenosine deaminase	hairy-cell leukemia
bortezomib	peptide analog	proteasomal degradation	multiple myeloma
paclitaxel	natural product ^a	microtubule destabilization	lung, ovarian, breast cancer
etoposide	natural product ^a	DNA unwinding	lung cancer, sarcomas, glioblastoma
mitoxantrone	topoisomerase inhibitor	DNA unwinding	AML, breast cancer, NHL
irinotecan	topoisomerase inhibitor	DNA unwinding	colorectal carcinoma
vinblastine	natural product ^a	microtubule assembly	Hodgkin's lymphoma
vorinostat	hydroxamic acid	histone deacetylation	cutaneous T-cell lymphoma
azacitidine	pyrimidine analog	DNA methylation	myelodysplastic syndrome

Abbreviations: NHL, non-Hodgkin's lymphoma; AML, acute myelogenous leukemia.

^aComplex structure.

Chemotherapeutic drug in combination

Table 16.4 Examples of multi-drug treatment protocols

Acronym	Components	Mechanisms of action	Application
ABVD	doxorubicin, bleomycin, vinblastine, dacarbazine	intercalation, DNA strand breaks, microtubule inhibition	Hodgkin's lymphoma
CHOP	cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone	alkylating, DNA intercalation, microtubule inhibition, steroid antagonist	non-Hodgkin's lymphoma
FOLFOX	fluorouracil, leucovorin, oxaliplatin	pyrimidine analog, folic acid antagonist, DNA cross-linking	colorectal cancer
TIP	paclitaxel, ifosfamide, platinum agent cisplatin	microtubule antagonist, alkylating, DNA cross-linking	testicular cancer

More specific cancer drug development

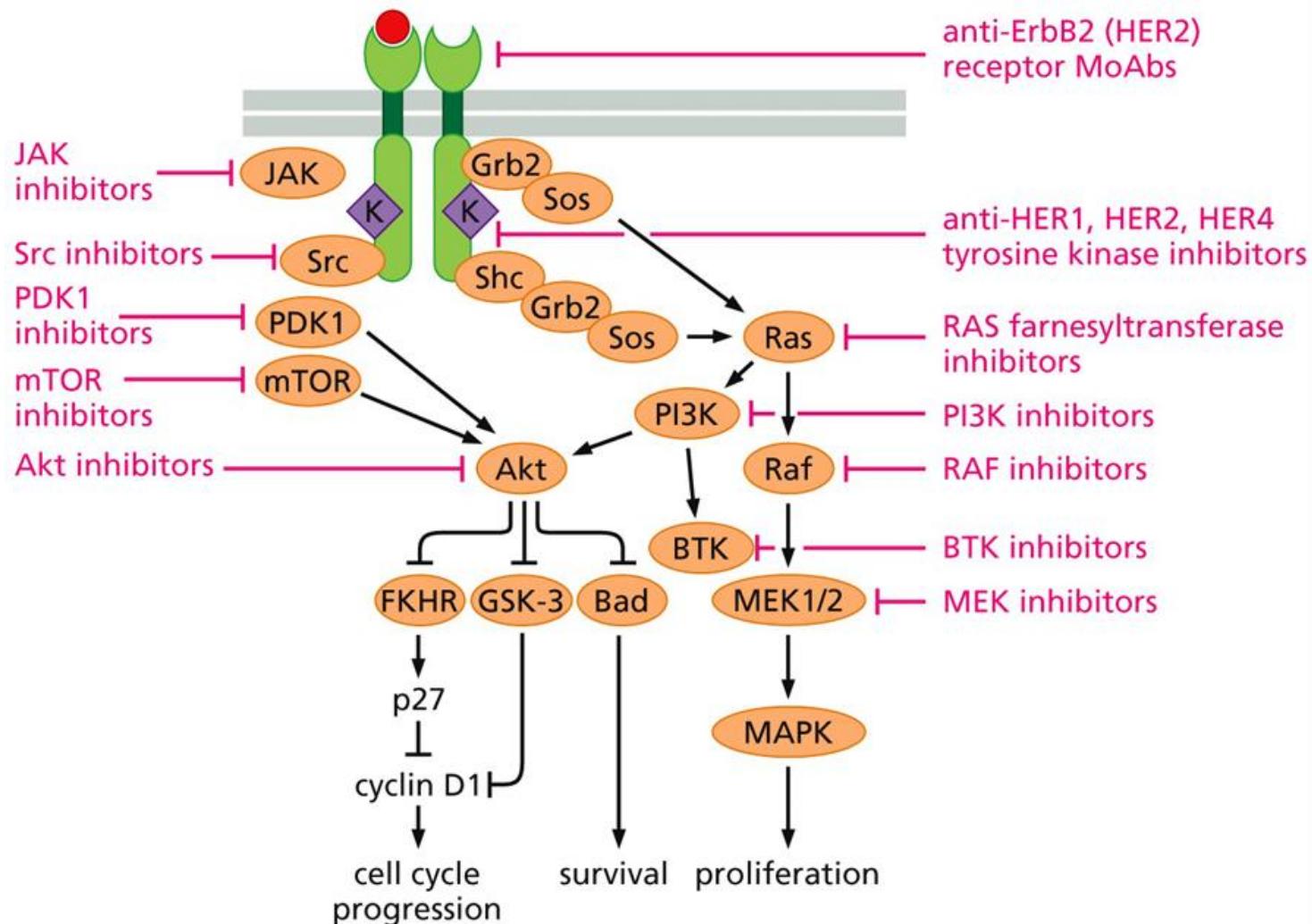


Figure 16.9 The Biology of Cancer (© Garland Science 2014)

The successful case of Gleevec

- Target BCR-Abl, which is the initiating oncogene to induce chronic myelogenous leukemia (CML), greatly increase the lifespan of this type of leukemia patients.

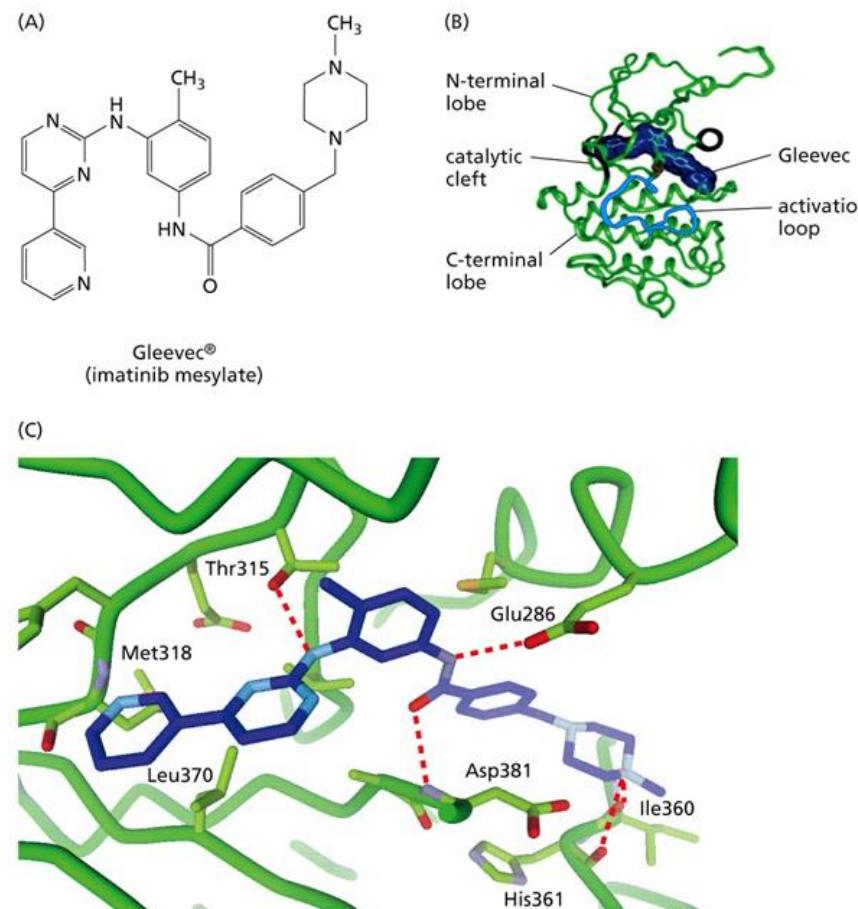


Figure 16.10 The Biology of Cancer (© Garland Science 2014)

- Gleevec more specifically targets BCR-Abl versus other kinases

All kinase folds are similar

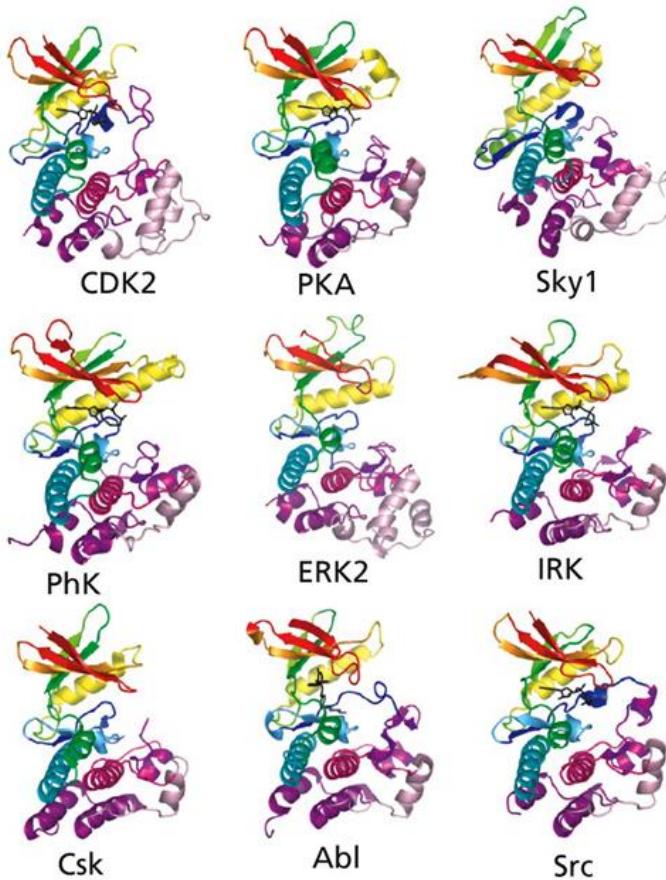


Figure 16.12a The Biology of Cancer (© Garland Science 2014)

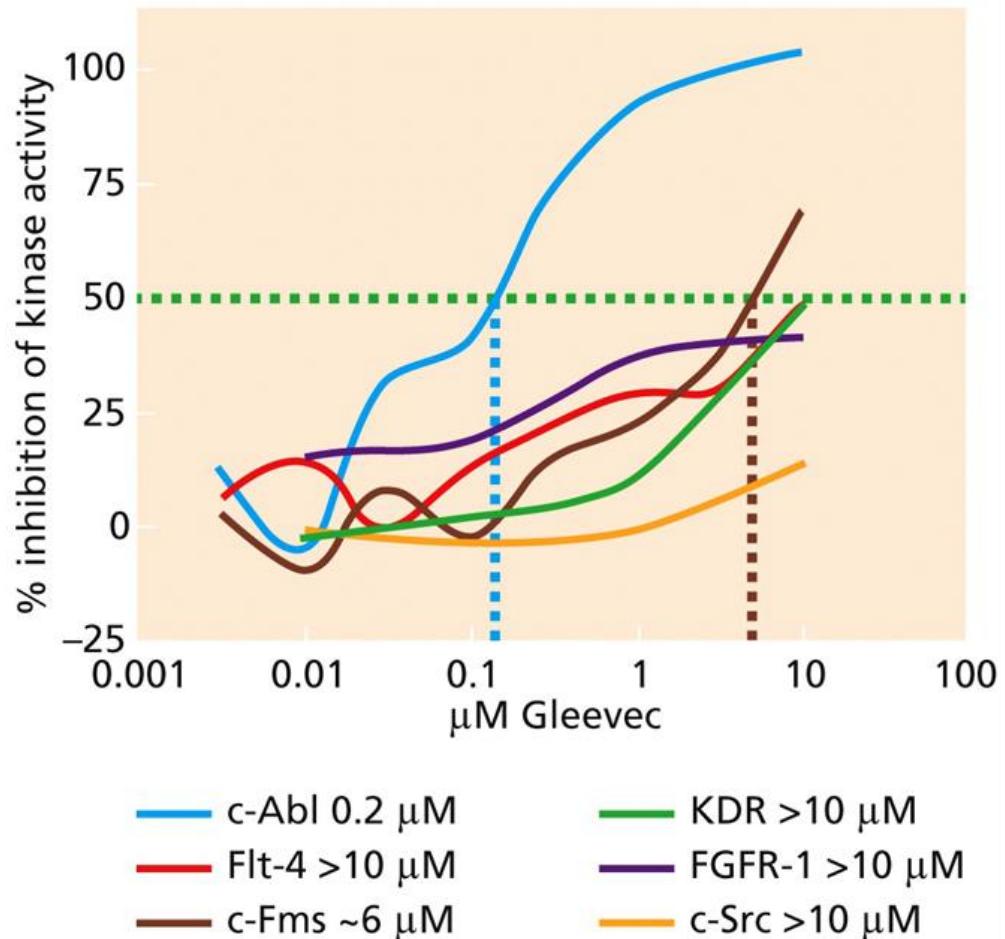


Figure 16.14 The Biology of Cancer (© Garland Science 2014)

Over the time, cancer develop resistance to cancer drugs...

Table 16.5 Mechanisms of acquired resistance to anti-cancer therapies^a

Nature of resistance	Mechanism of resistance
Multi-drug resistance ^b	increased expression of drug export pumps
Pan-drug resistance ^c	unknown
Drug detoxification ^d	enzymatic detoxification of drug molecule
Acquired drug resistance	refuge of cancer cells in drug-protected anatomical sites ^e failure of tissue to convert pro-drug into active form refuge of cancer cells in an anatomical site that provides protective trophic signals ^f massive stromalization ^g emergence of mutant, structurally altered cellular target ^h amplification of gene encoding targeted protein emergence of cells bearing alterations in genes whose products are functionally redundant with drug target ⁱ loss of drug importer ^j passage through an EMT ^k activation of anti-apoptotic regulators
Physiologic activation of compensatory adaptive mechanisms	
Resistance to EGF-R inhibition	up-regulation of IGF-1R signaling amplification of <i>Met</i> gene mutational activation of a <i>ras</i> gene
Resistance to Smoothened inhibition	amplification of <i>Gli2</i> gene
Resistance to Bcr-Abl inhibition	amplification of <i>Bcr-Abl</i> gene

^aThe entries in this table refer to tumors that are initially responsive to an applied therapy and then exhibit resistance that is manifested as regrowth of a tumor and thus indicates clinical relapse. Resistance may emerge because of the outgrowth of a therapy-resistant subpopulation of variant cells; such variant cells may preexist in the population prior to the onset of treatment or may arise as genetic or epigenetic variants that are formed *de novo* during the course of treatment. Alternatively, resistance may arise as a normal compensatory physiologic response to an initially applied therapy-imposed inhibition; this second form of resistance presumably occurs widely throughout a tumor rather than resulting from the selective outgrowth of a therapy-resistance subpopulation.

^bAs an example, concomitant resistance to paclitaxel, doxorubicin, etoposide, and vinblastine is exhibited by cells overexpressing P-glycoprotein, a drug export transporter operating in the plasma membrane.

^cPan-drug resistance refers to resistance against all agents that are applied to a tumor and cannot be attributed to increased drug export.

^dAs an example, lack of responsiveness of glioblastomas to the temozolamide alkylating drug is often due to expression of the MGMT enzyme, which detoxifies it (see Section 12.8).

^eAs an example, a variety of metastatic growths in the brain may be protected from chemotherapy by the blood-brain barrier, which blocks agents in the circulation from entering the brain parenchyma.

^fAs an example, lymphoma cells may survive in the thymus because thymic stromal cells release survival factors in response to the genotoxic stress provoked by chemotherapy.

^gAs an example, part of the difficulty of treating pancreatic carcinomas derives from the development in these tumors of a highly desmoplastic stroma that impedes transport of drugs from the circulation to the neoplastic cells.

^hAs an example, patients treated successfully with imatinib/Gleevec will develop drug resistance because of the emergence of cells expressing a mutant, structurally altered Bcr-Abl protein that no longer permits high-affinity binding of the drug.

ⁱAs examples, individuals whose tumors exhibit responsiveness to EGF-R inhibitors may develop resistance because of the mutational activation of a *ras* oncogene or because of *crl* amplification. Resistance of CML cells to imatinib/Gleevec may develop because of the emergence of cells expressing altered p19^{ARF}, Myc, p53, or Ras, which function to bypass the dependence of the tumor cells on the targeted Bcr-Abl oncoprotein. Resistance to B-Raf inhibition can develop through up-regulation of PDGF-R β expression or N-ras mutation.

^jHigh-grade serous ovarian carcinomas are often treated with doxorubicin that is encapsulated in a synthetic liposome. Drug-resistant cells often emerge that have lost the LDL receptor-related protein (LRP1B), a cell surface protein that appears to be responsible for internalizing the liposomes.

^kPassage through an epithelial-mesenchymal transition (EMT) results in, among other changes, the expression of drug efflux pumps in the plasma membrane and increases in expression of anti-apoptotic proteins.

Cancer immunotherapy

Reactivation of immune system in cancer patients
to inhibit cancer development

Two examples:

1. CAR-T (chimeric antigen receptor- T cell)
2. Anti-PD1 antibody

Emily Whitehead

CD19-CAR-T therapy



03/2013, NEJM



2017-12-1

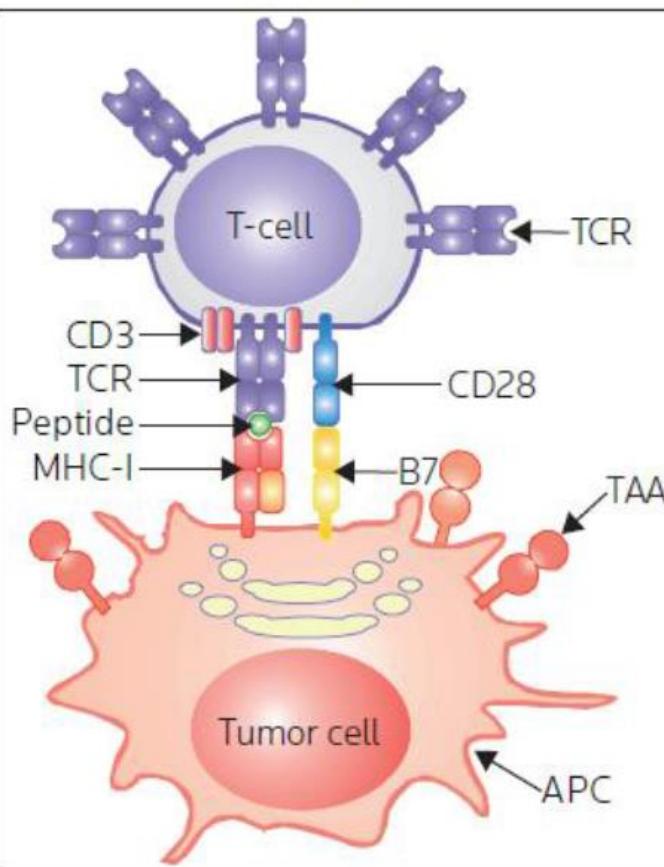
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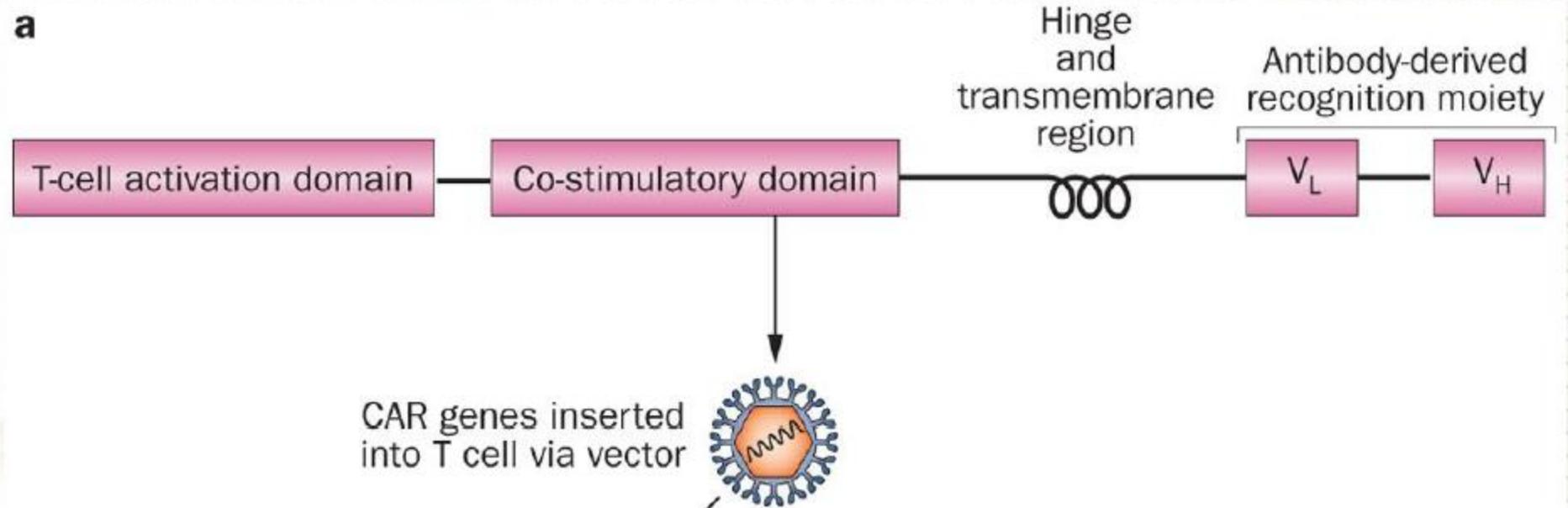
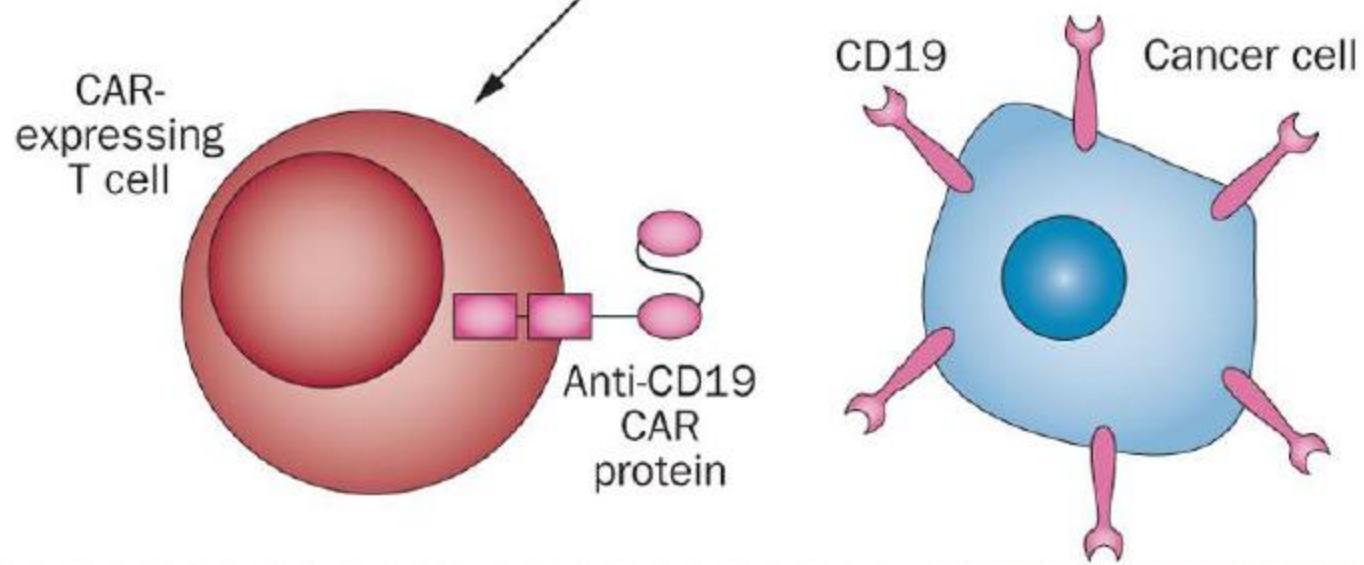
CANCER IMMUNOTHERAPY

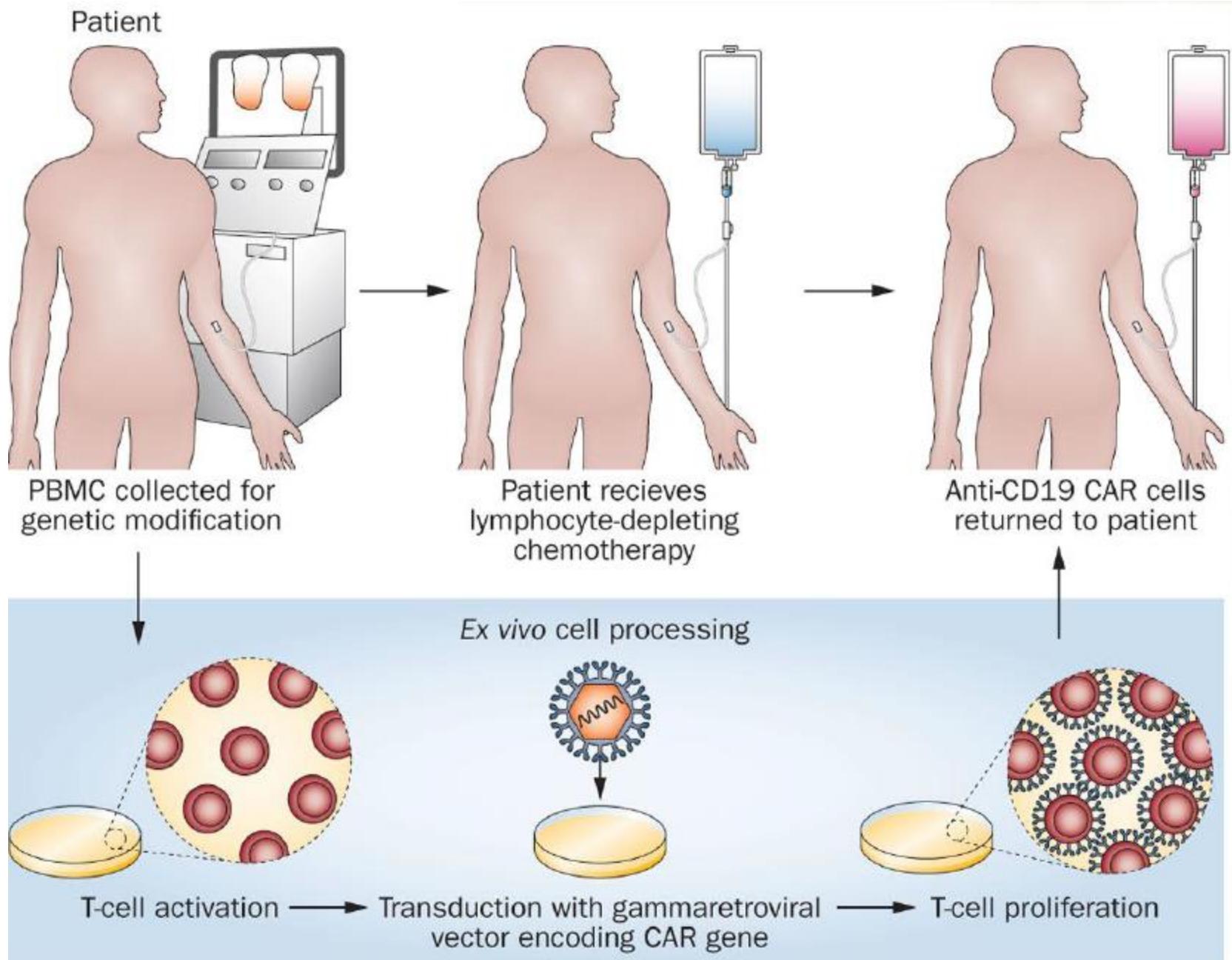
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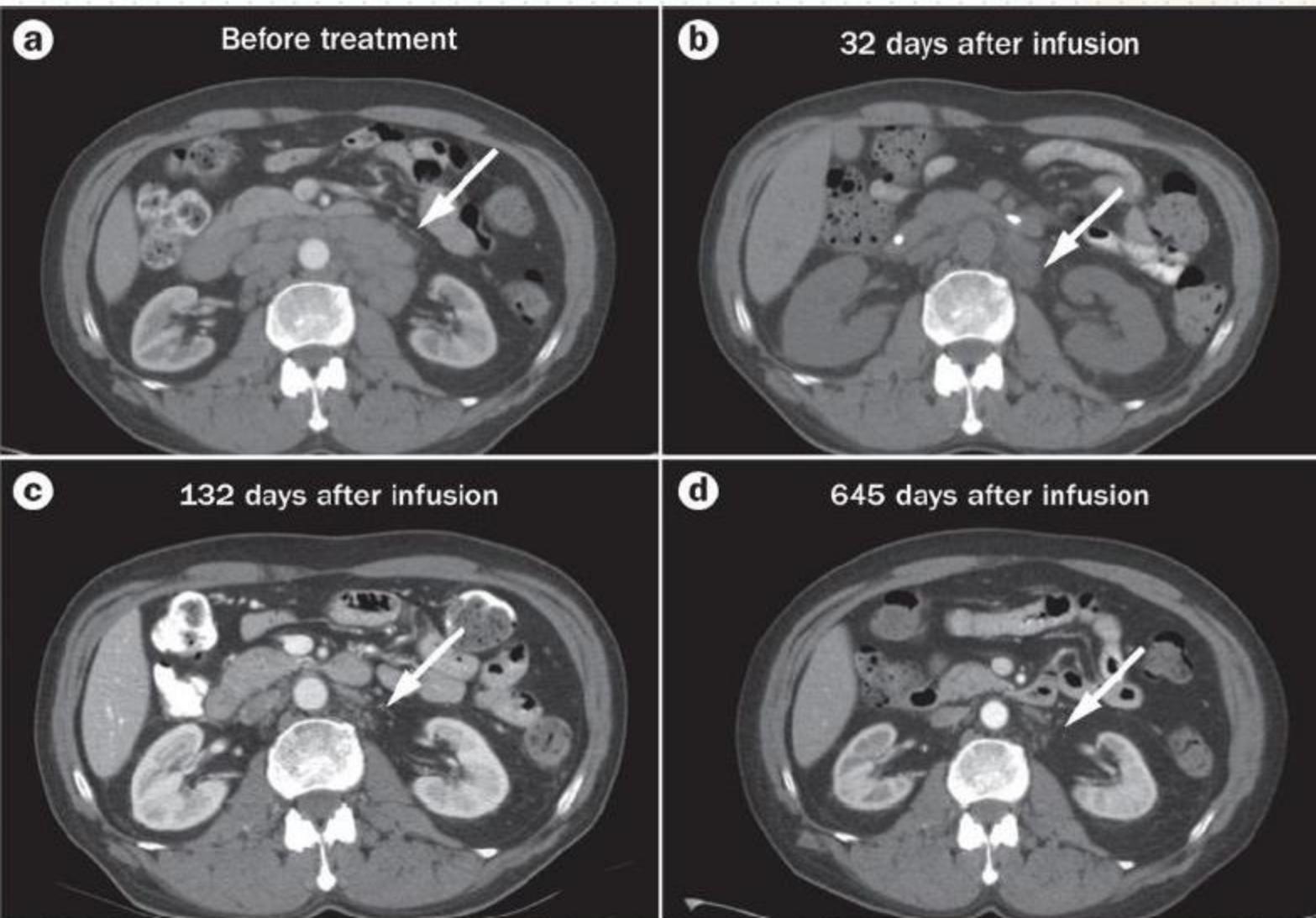


Elements required for specific T-cell response

- Specific T-cell receptor
- Peptide antigen presentation and processing
- MHC-I/ β_2 -microglobulin
- Costimulatory molecules

a**b**





Anti-PD-1 as a immunotherapy for tumors

