

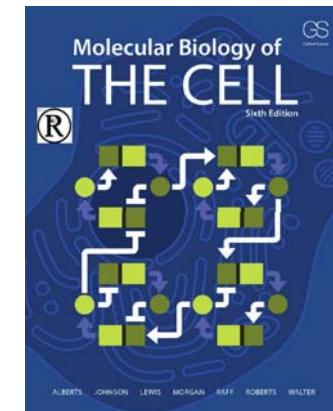
Lecture 20

Cancer Biology

Outline

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

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Chapter 20

Before we start we have to learn some new terms first...

Why is cancer called cancer?

- The Greek physician **Hippocrates** (460-370 BC), the “Father of Medicine” used the terms ***carcinos*** and ***carcinoma*** to describe non-ulcer forming and ulcer-forming tumors.
In Greek, this means a **crab**.
- The description was named after the crab because the finger-like spreading projections from a cancer called to mind the shape of a crab.
- Later, Roman physician, **Celsus** (28-50 BC) translated the Greek term into cancer, the **Latin** word for **crab**.
- It was **Galen** (130-200 AD), another Roman physician, who used the term ***oncos*** (**Greek for swelling**) to **describe tumors**.
Oncos is the root word for **oncology** or study of cancers.

Before we start we have to learn some new terms first...

What is cancer?

- The term **cancer** specifically refers to a **new growth**, that:
 - has the **ability to invade** surrounding tissues,
 - **might metastasize** (spread to distant other organs) and
 - eventually **may lead to** death (if untreated).

What is a tumor?

- “**Tumor**” is a commonly used, but non-specific, term for **neoplasm**, the **abnormal new growth of cells**.
- The word “**tumor**” simply **refers to a mass**.
- This is a general term that can refer to **benign (generally harmless)** or **malignant (cancerous) growths**.

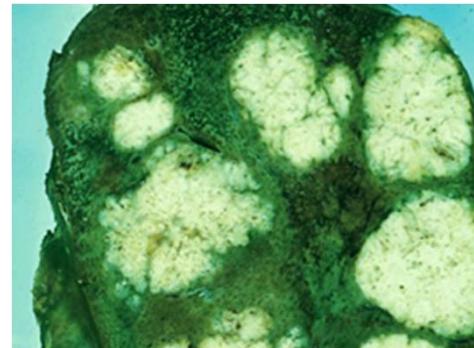
I. The nature of cancer

Metastases: destructive abnormal new growth

Metastases are secondary tumors that grow and destroy the surrounding tissue



Metastases
(lung, mouse)

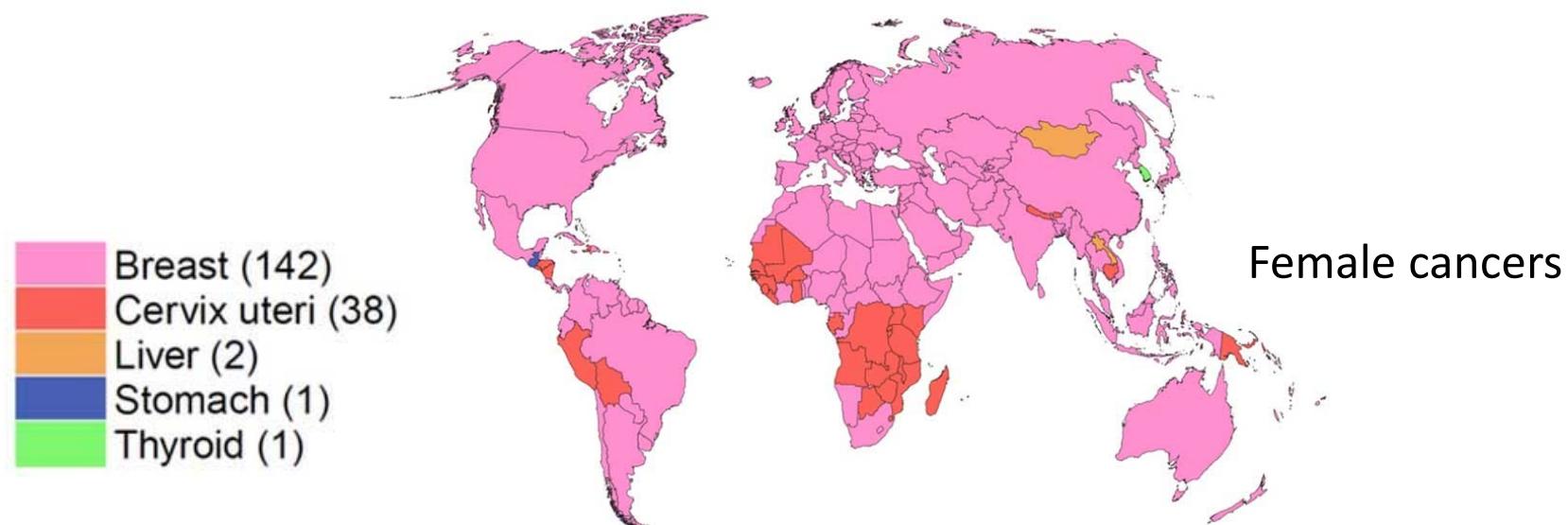
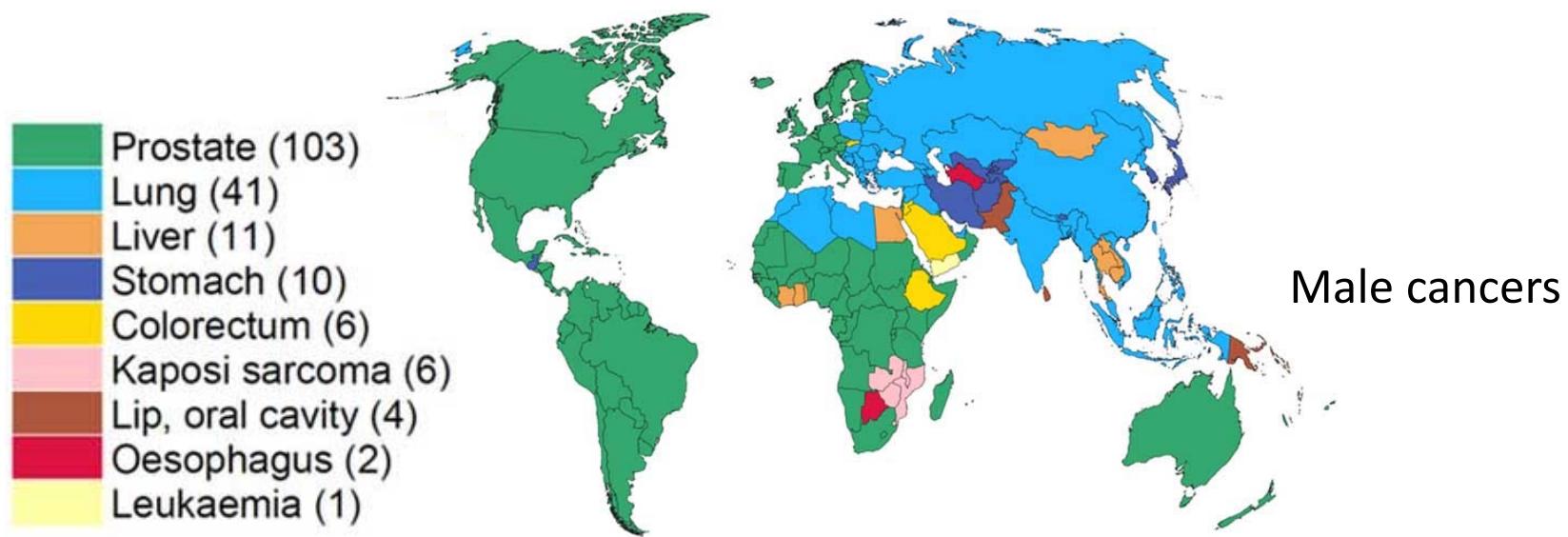


Metastases
(liver)

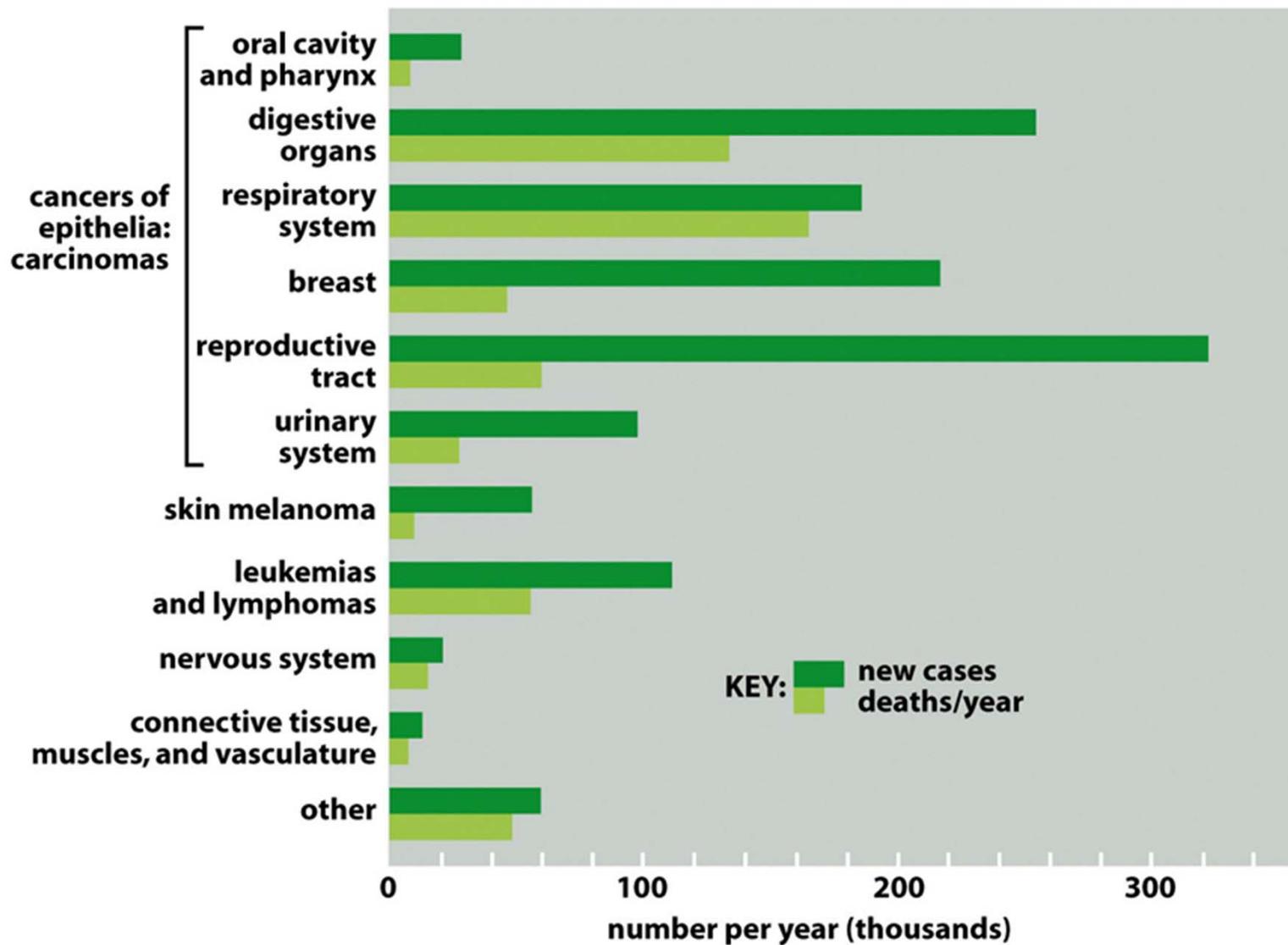


Metastases
(brain)

World wide cancer statistics



Cancer incidences and mortalities in the United States in 2012



What is cancer? More terms and definitions...

Definition of cancer:

- Cancer cells are cells that **grow beyond limitations**
- The cells **grow out of control** and they **have sustaining proliferating potential** ("eternal life")
- Cells are **able to invade** distant organs

Different types of tumors:

- Primary tumor versus metastasis
 - **Primary tumor:**
Is the initial tumor, the starting point of the cancer growth
 - **Metastasis:**
Is a new settlement of tumor forming cells, which are derived from another, primary tumor. Also referred to as secondary tumor

Benign tumor versus malignant tumor:

- **Benign tumor:**
Tumors that grow locally but **do not invade (spread)**
- **Malignant tumor:** tumors that **invade** other distant tissues/organs

Tissue images of cancer

Epithelial cancers: Cervix intraepithelia neoplasia (CIN)

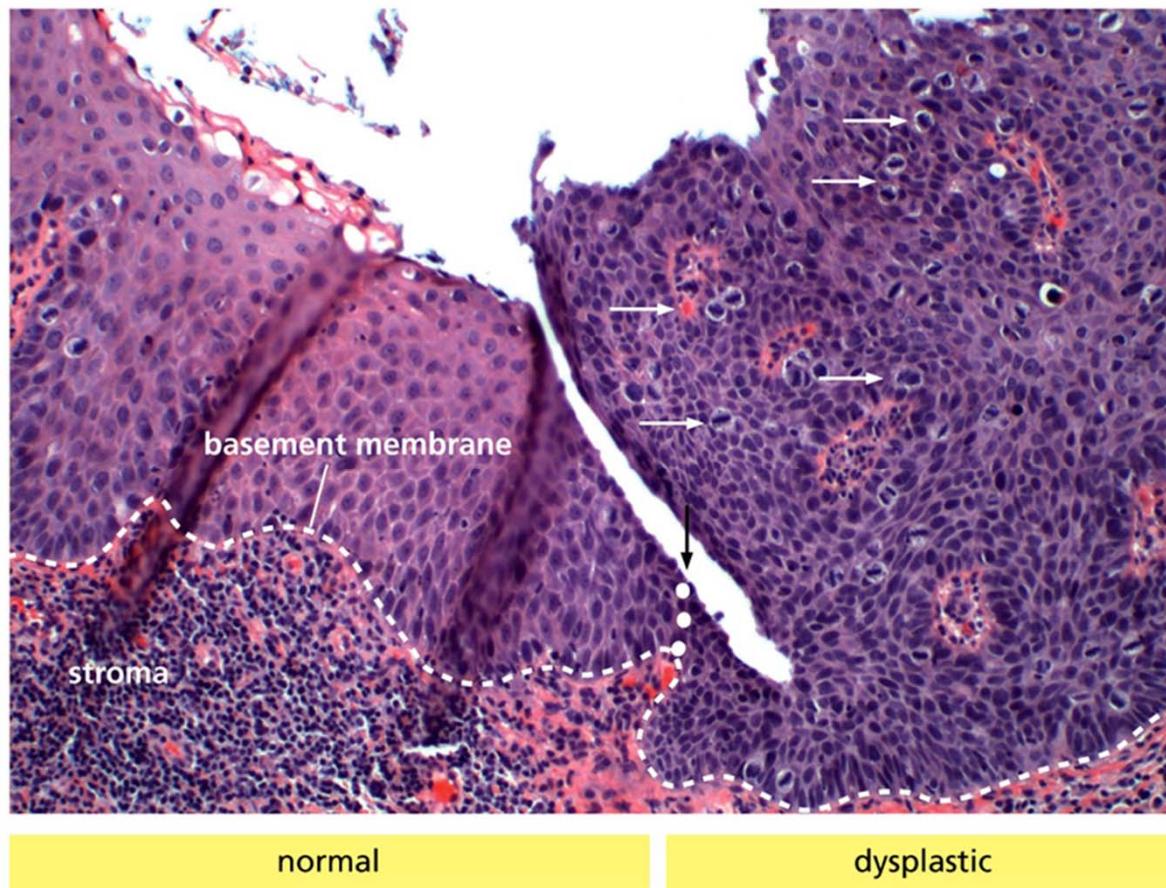


Figure 2.15 The Biology of Cancer (© Garland Science 2014)

Normal versus hyperplasia epithelium in the duct of mammary gland

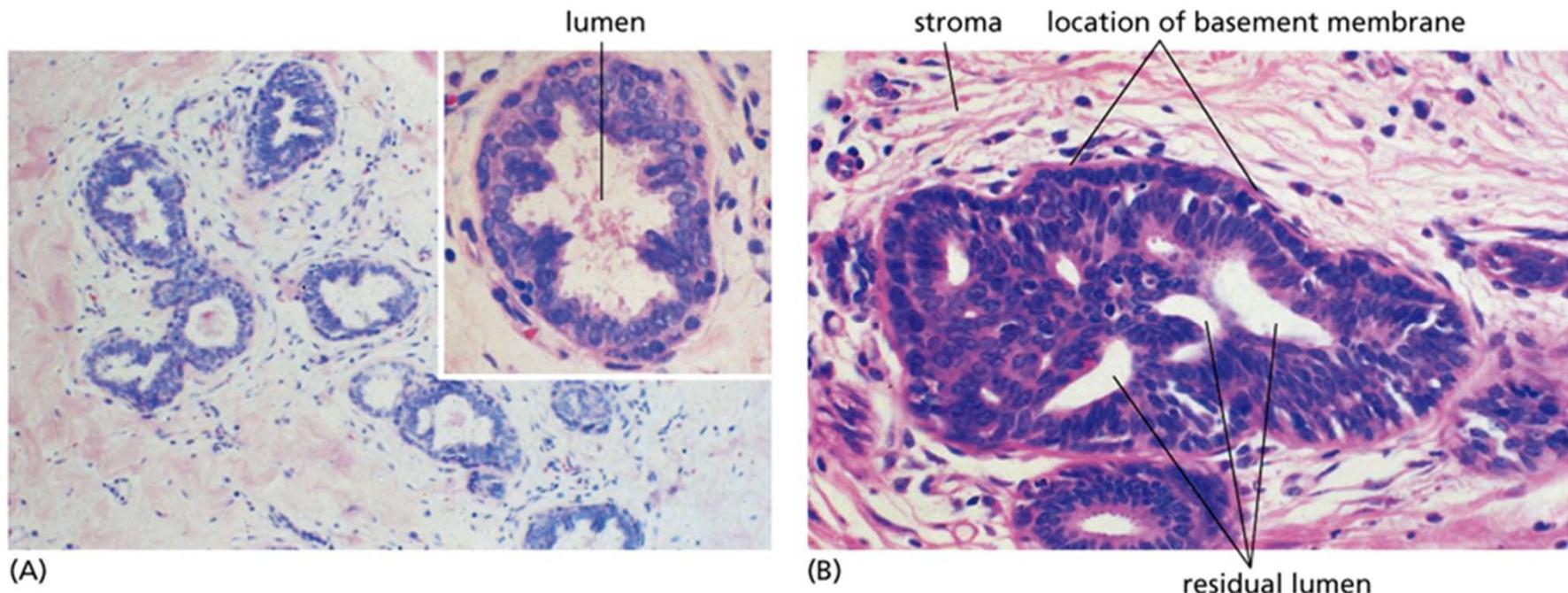


Figure 2.13 The Biology of Cancer (© Garland Science 2014)

Osteosarcoma

Mesenchymal tumors

- The osteosarcoma seen here has **malignant bone-forming cells** (osteoblasts with dark purple nuclei), growing amid mineralized bone (*pink*)
- The tissue has been constructed by these osteoblasts in the surrounding extracellular matrix.

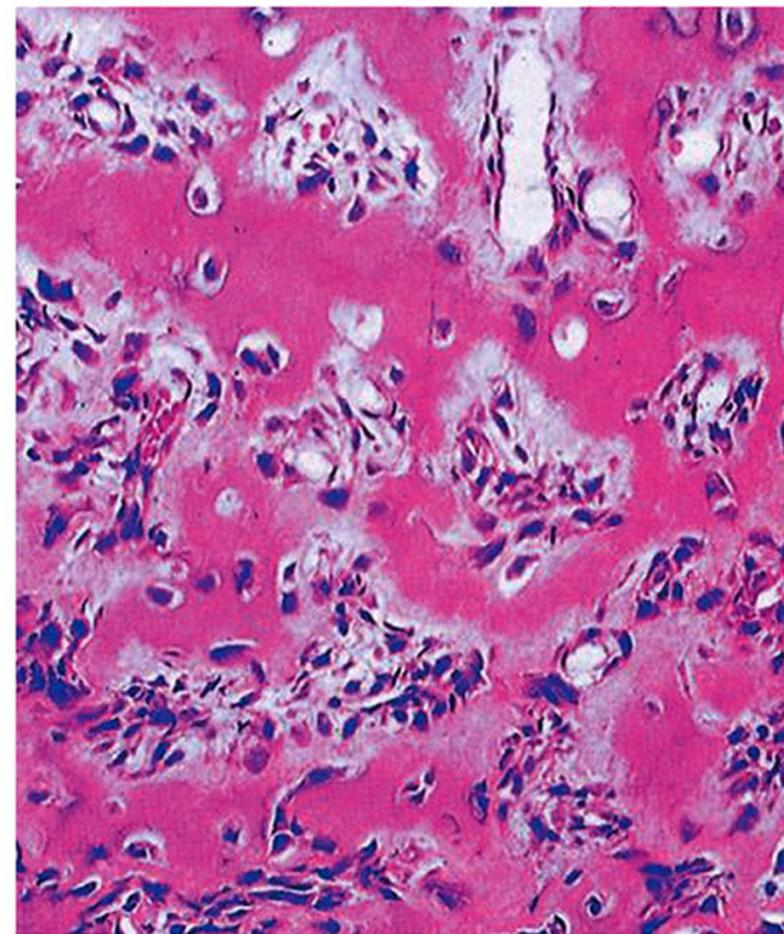
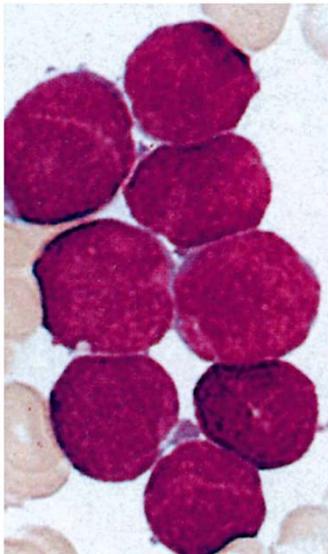


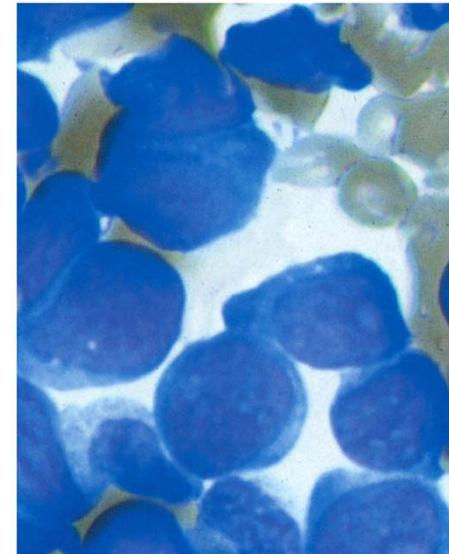
Figure 2.7a The Biology of Cancer (© Garland Science 2014)

Cancers from blood forming tissues: Hematopoietic malignancies

ALL (acute lymphocytic leukemia)



AML (acute myelogenous leukemia)

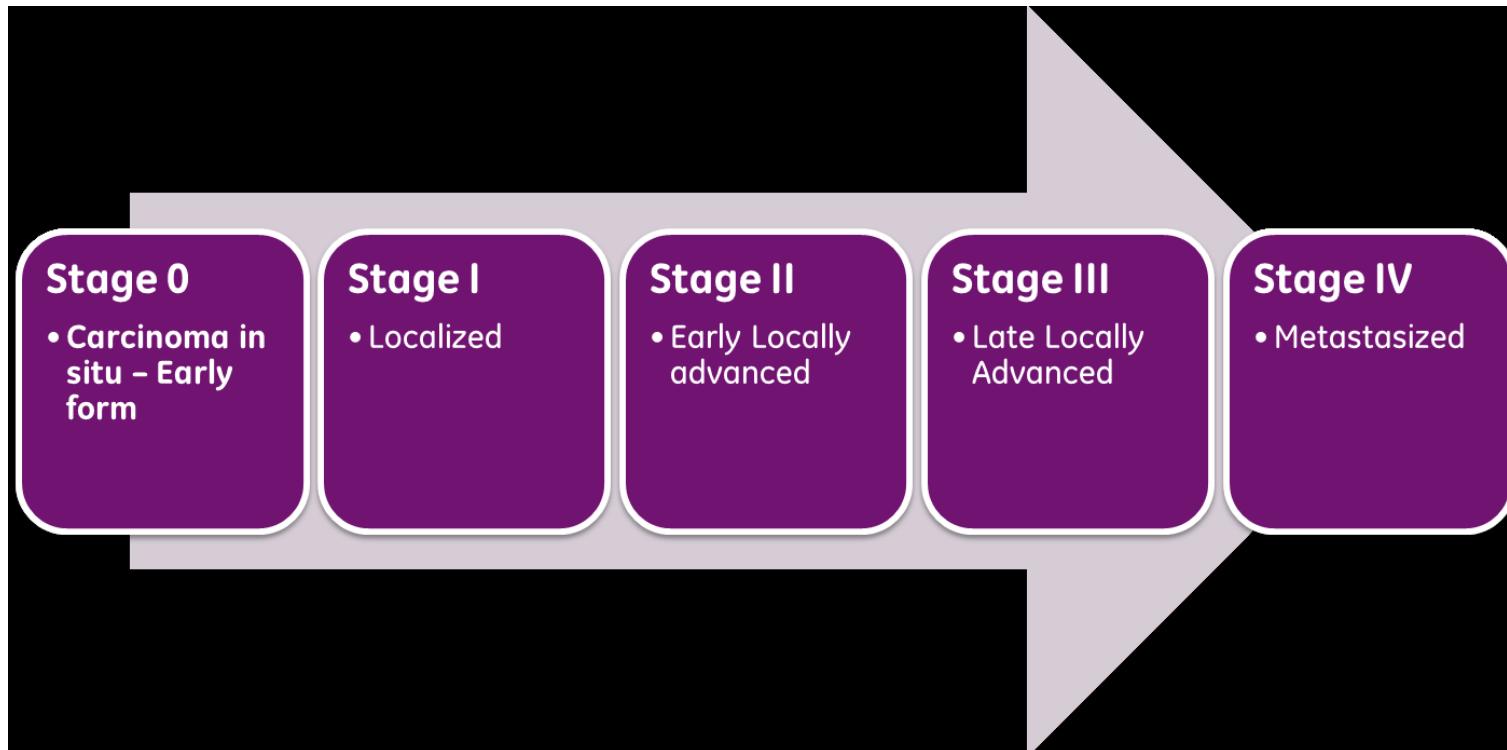


ALLs arise from both the B-cell (80%) and T-cell (20%) lineages of lymphocytes. The cells forming this particular tumor **exhibited the antigenic markers** indicating origin from pre-B cells.

As in many hematopoietic malignancies, **AML cells** have only a **small rim of cytoplasm** around their **large nuclei**. They derive from precursor cells of the lineage that forms various types of granulocytes as well as monocytes, the latter developing into macrophages.

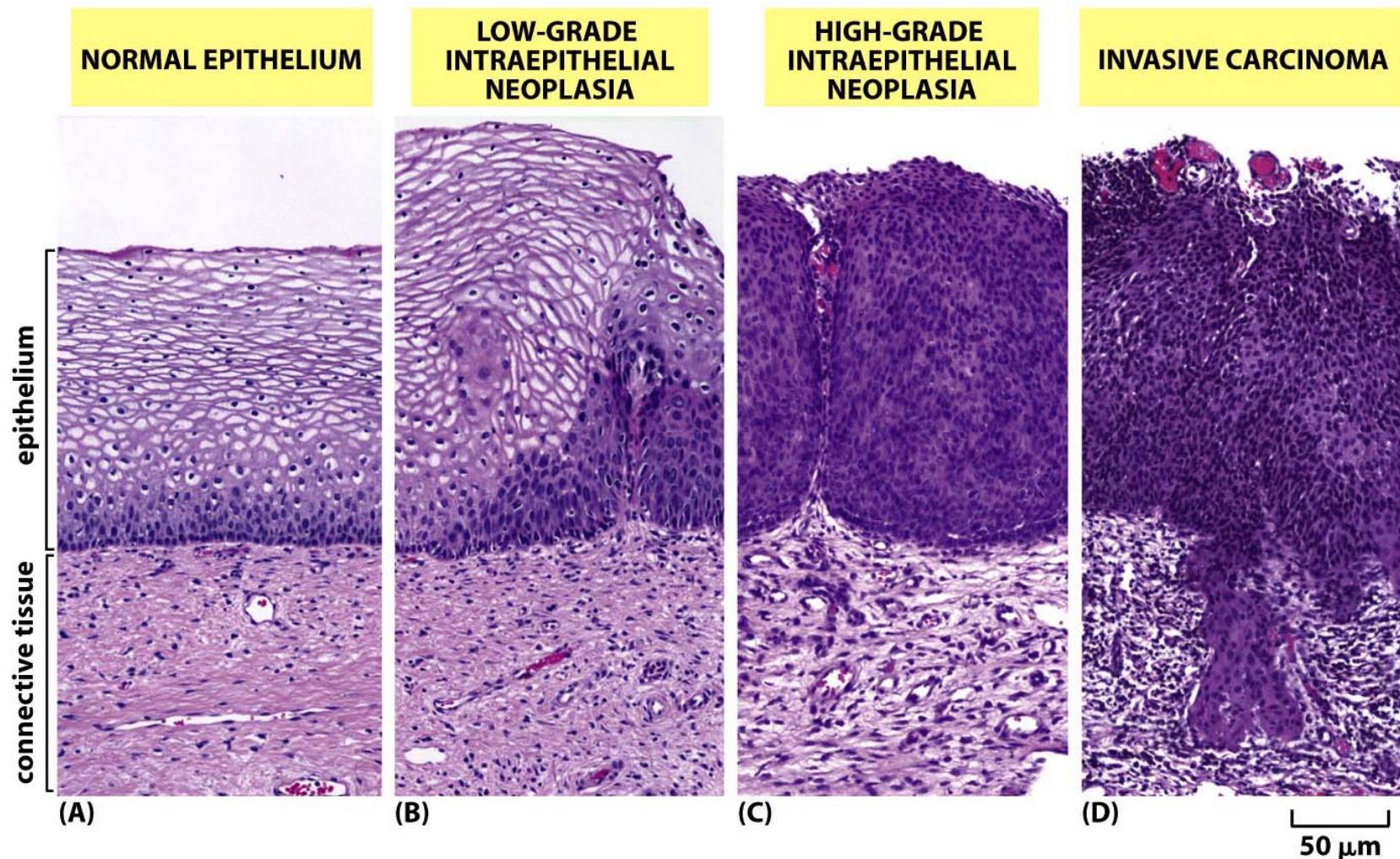
Categories and stages of tumors

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



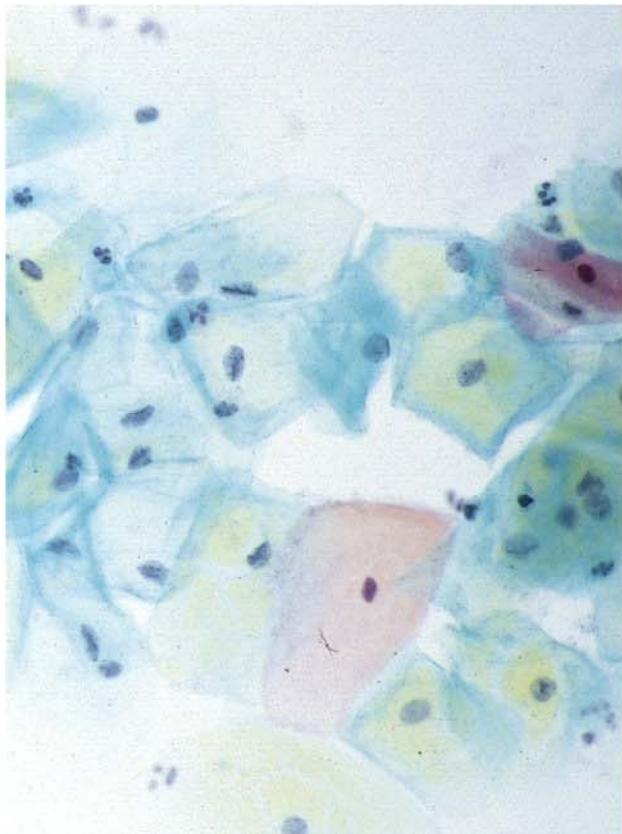
Stages of progression in the development of cancer

Cancer of the stratified squamous epithelium of the uterine cervix

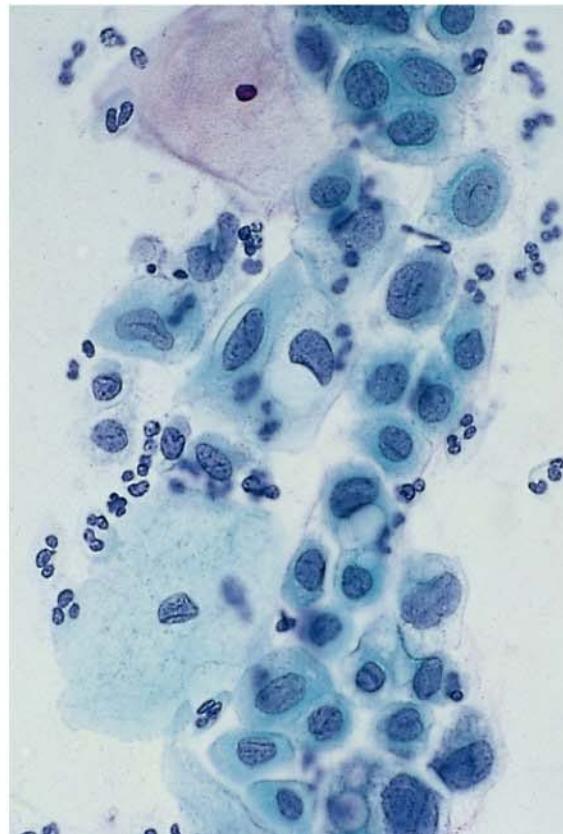


Differences between normal and cancerous cells:

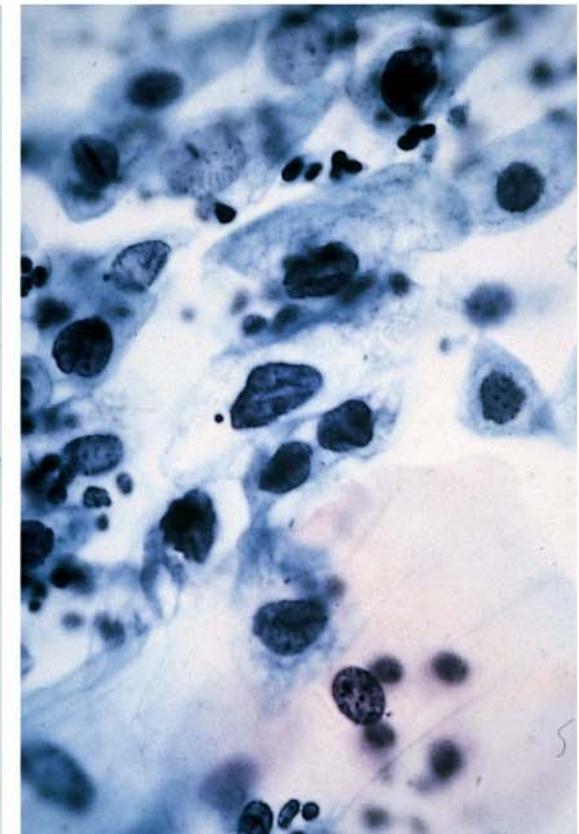
Normal cells
with
highly condensed
nucleus



Precancerous lesions,
still differentiated cells,
not yet invasive



Invasive carcinoma,
undifferentiated cells, little
cytoplasm, large nucleus



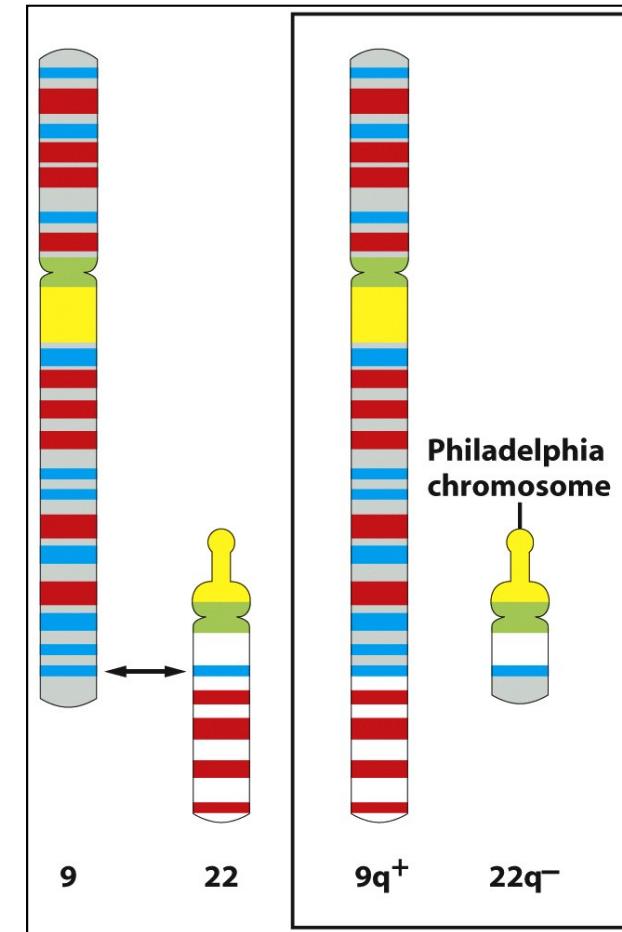
II. Features of cancer: monoclonal origin/clonal descentance

How to proof monoclonal origin of cancer?

Molecular analysis of chromosomes reveals the clonal descentance of the cancer cells.

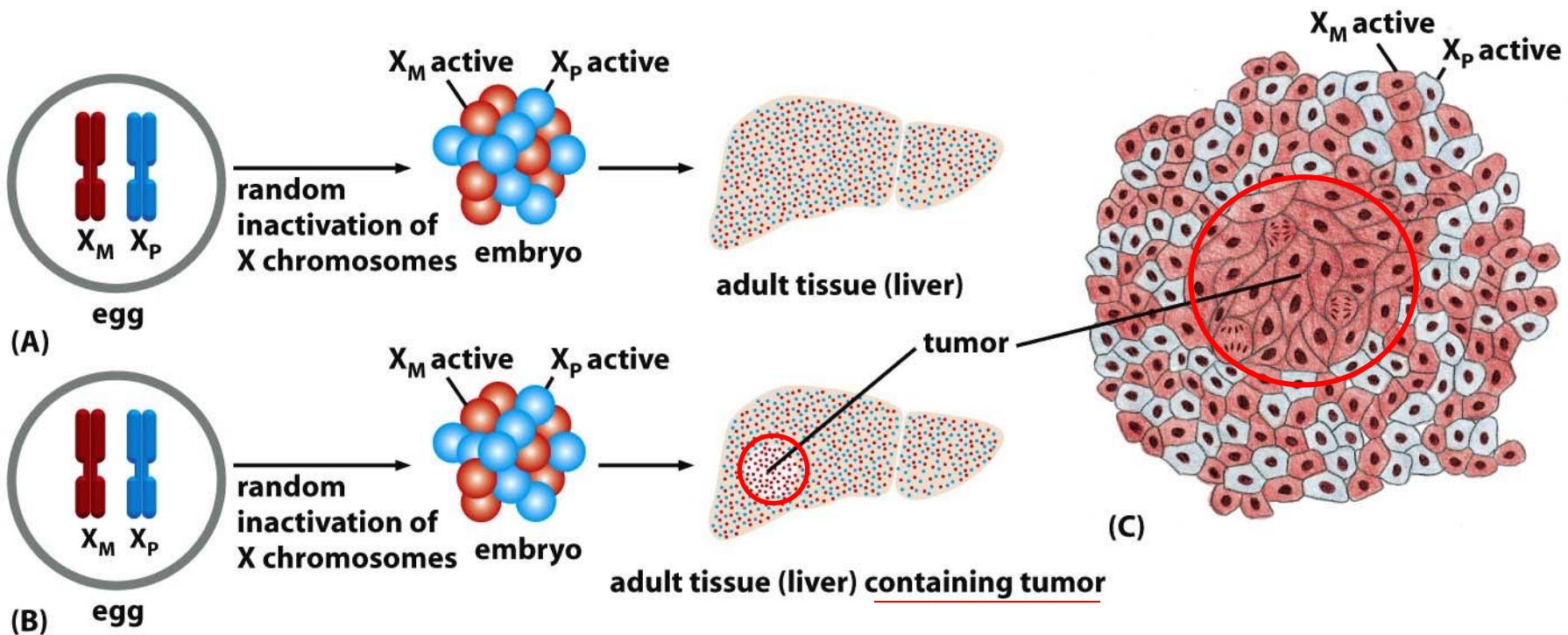
Example: Chronic myelogenous leukemia (CML)

- In CML, all cancer cells have generally the same translocation of the chromosome between the **long arms of chromosomes 9 & 22 (Philadelphia chromosome)**
- However, the break & rejoin **differs** a few 100-100 bases between patients, **indicating an individual event in each case**



II. Features of cancer: monoclonal origin/clonal descent

Proof of monoclonal origin of cancer by X-inactivation mosaics within tumor tissue



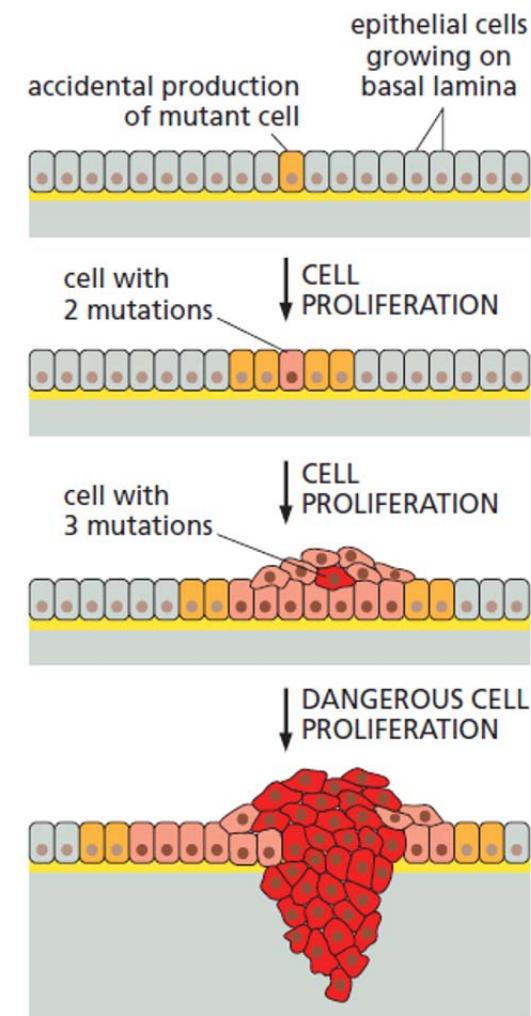
Somatic mutations in cancer - clonal evolution

Initiation of cancer is usually driven by multiple mutations

Development of a tumor by repeated rounds of mutations:

- each mutation either **enhances cell proliferation or decreases cell death**
- the progeny of such cells become the dominant clone in the tumor
- each step enhances the chance to proceed to the next step by increasing the numbers of cells that are at risk
- The final step: Invasion through the basement membrane - the initial step in metastasis

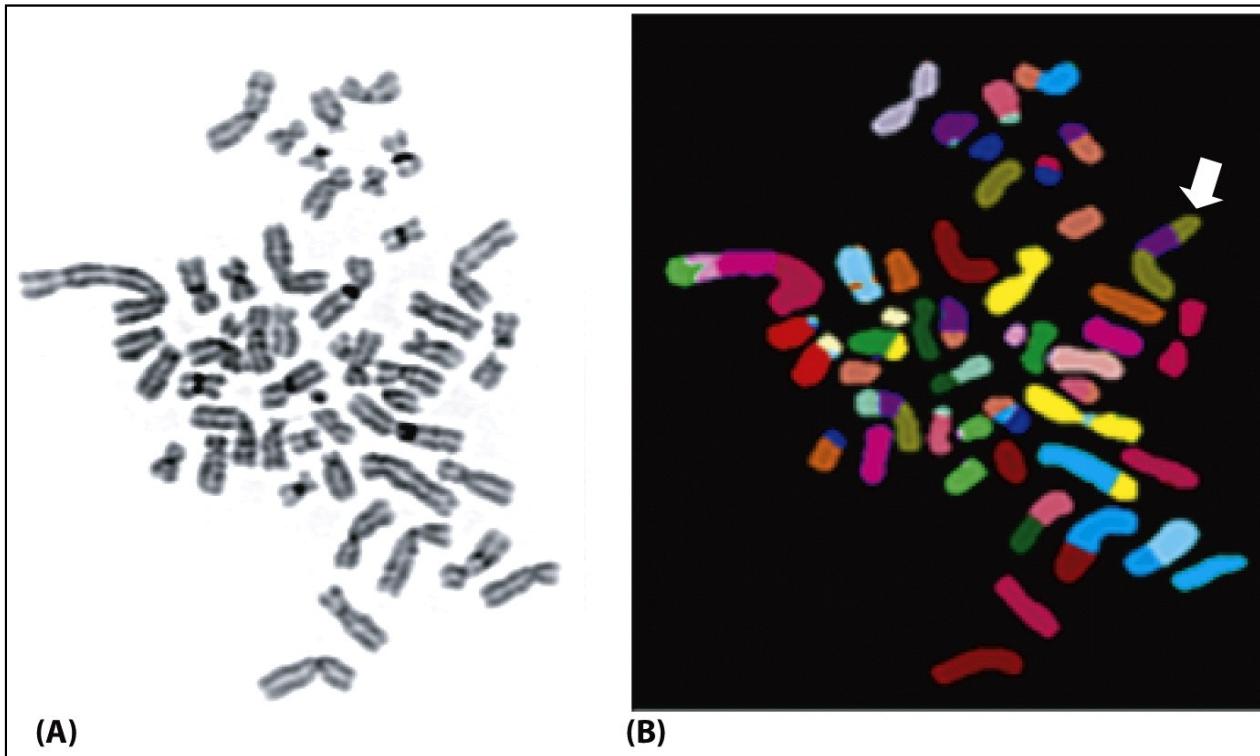
In reality, there are more than the three steps shown here, and a combination of genetic and epigenetic changes are involved



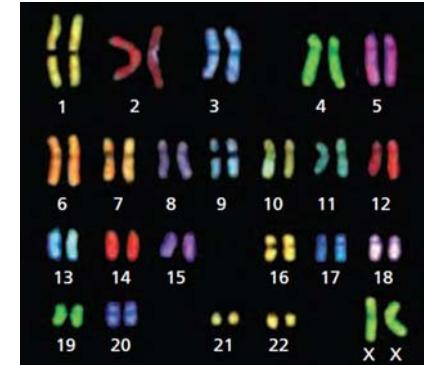
Cancer genomes are highly unstable

Polypliody, aneuploidy, translocations, etc.

Chromosomes from a tumor displaying abnormalities in structure & number:



Chromosome painting



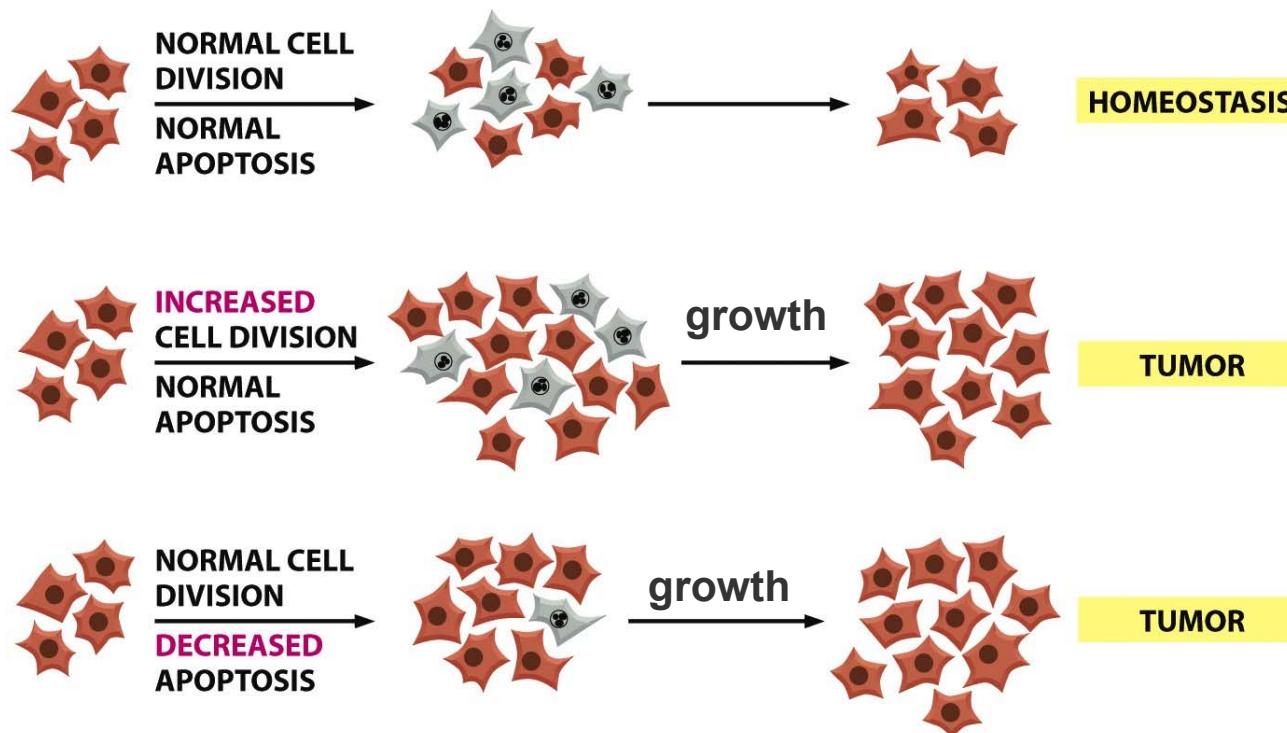
- The staining shows multiple translocations, including a **doubly translocated chromosome** (*white arrow*) that is made up of **two pieces of chromosome 8 (green-brown)** and a piece of **chromosome 17 (purple)**.
- The karyotype also contains 48 chromosomes, instead of the normal 46

Escape normal restrictions on proliferation potential

At normal conditions: Cell **division** and **apoptosis** is in **homeostasis**

Cancerous growth can be the result of

- Increased cell divisions
- Decreased apoptosis
- Both together



Abnormal responses to DNA damage and other stresses

Many conditions can result in the development of cancer:

A. DNA damage:

- p53 mutations
- ATM mutations
- failure to arrest cell cycle or/and failure to cause apoptosis:
each resulting in producing more genetic mutations in each cell cycle.

B. Warburg effects:

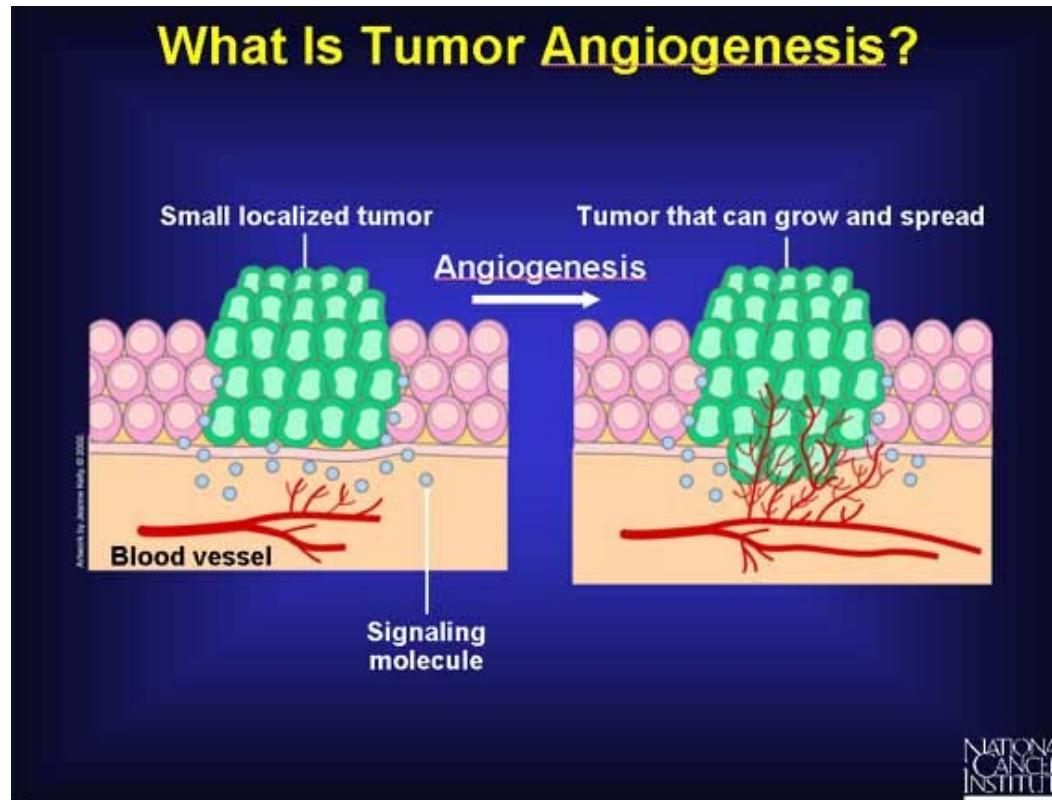
- increase glycolysis versus oxidative phosphorylation:
tumor tends to ferment.

C. Growth factor – independent

D. Failure to arrest cell cycle or to trigger apoptosis due to oncogene stress.

High activity of angiogenesis (formation of blood vessels)

Tumors induce the formation of new blood vessels to secure their own supply with oxygen and nutrients



But how does this work?

Angiogenesis: new formation of blood vessels

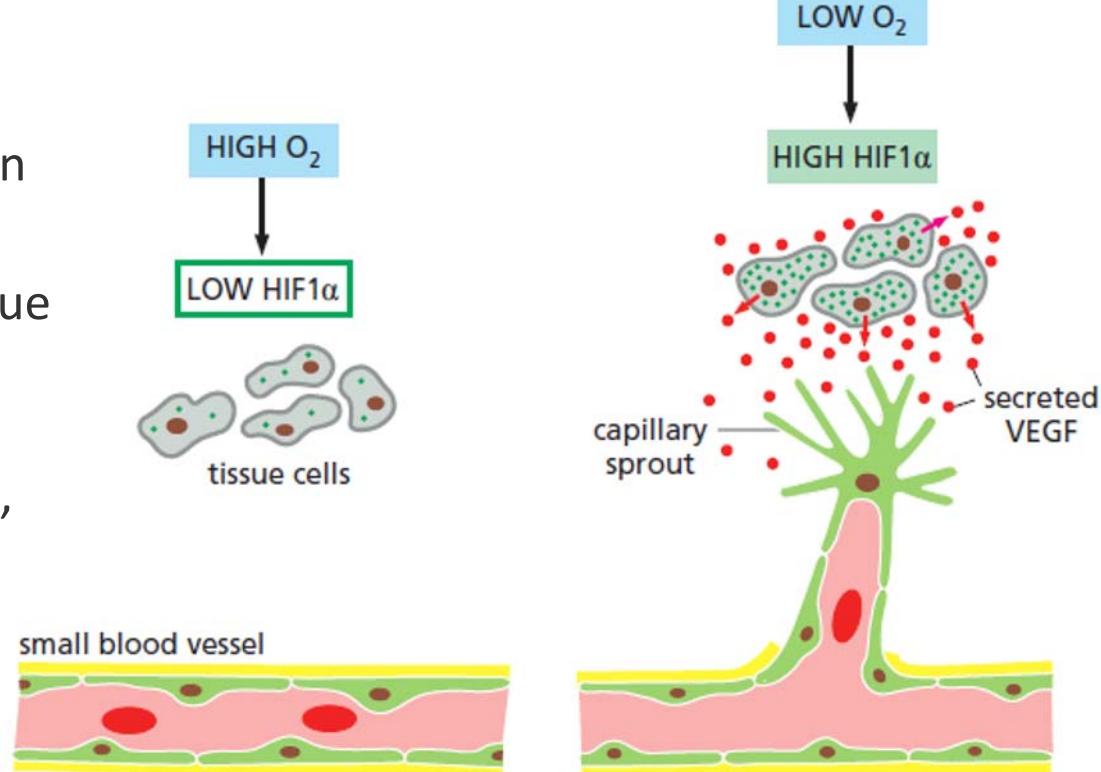
Cells sense the amount of available oxygen and nutrients.
If levels are too low, they call for supply...

The key players:

- VEGF (vascular endothelial growth factor) protein
- HIF1 α (hypoxia-inducible factor 1 α) transcription factor for VEGF

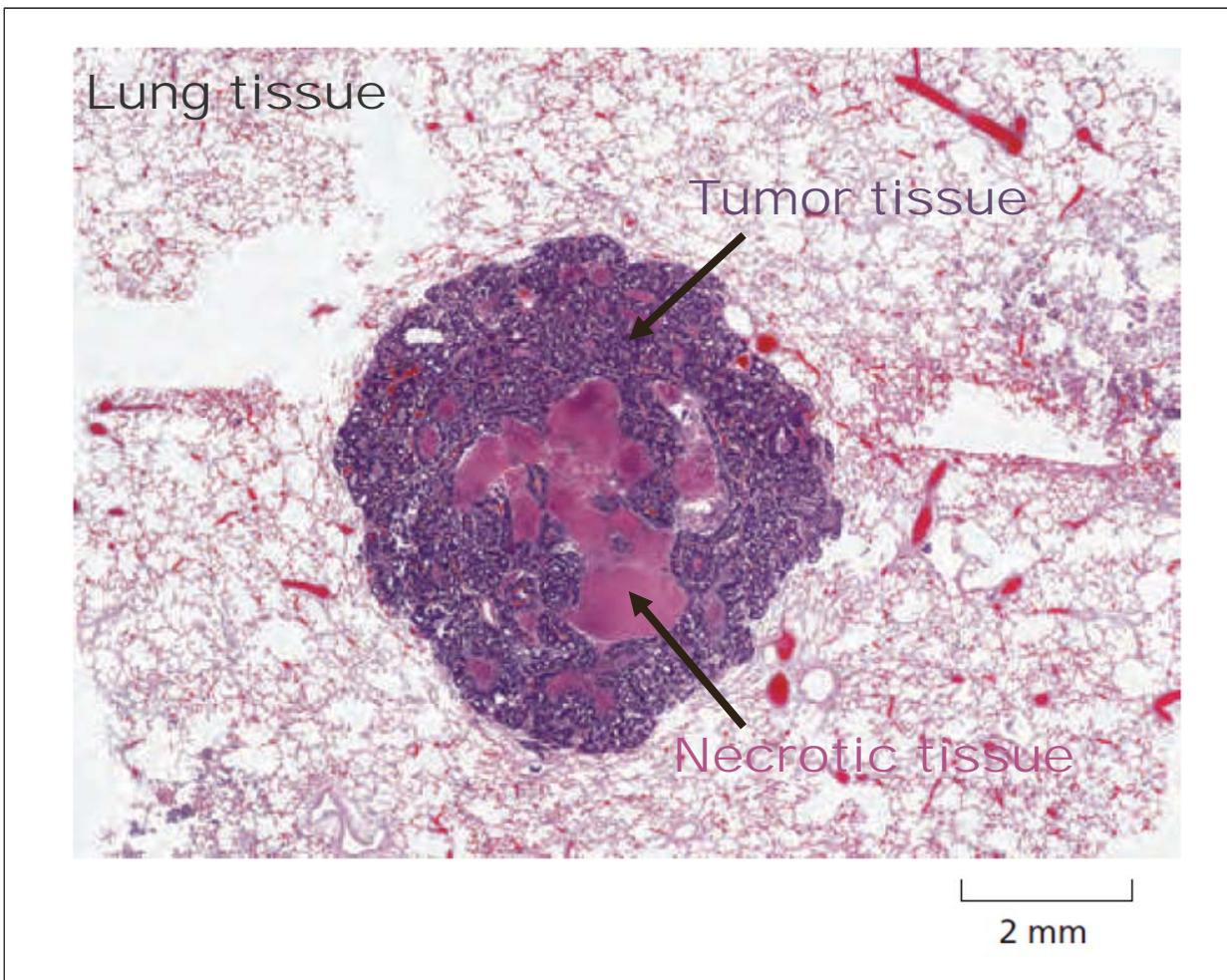
Mechanism:

- low oxygen increases intra-cellular levels of HIF1 α
- HIF1 α stimulates transcription of *Vegf*, raising VEGF levels
- VEGF is secreted into the tissue and reaches endothelial cells
- VEGF induces production of proteases in endothelial cells, allowing them to digest the basal lamina and to sprout towards the tumor



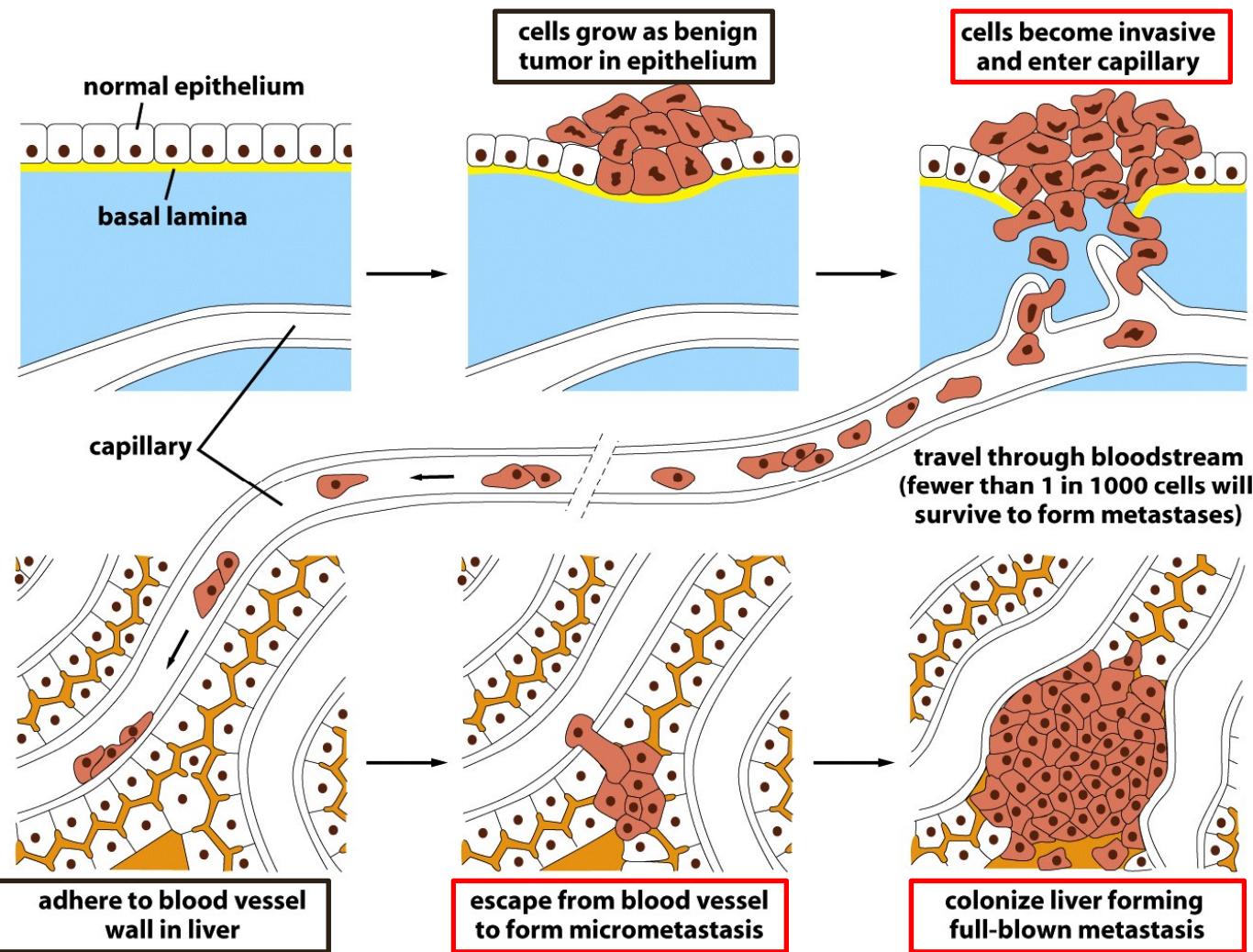
Angiogenesis: new formation of blood vessels

Cells sense the amount of available oxygen and nutrients.
If levels are too low, they call for supply. Otherwise, they die...



Metastasis: The fatal step

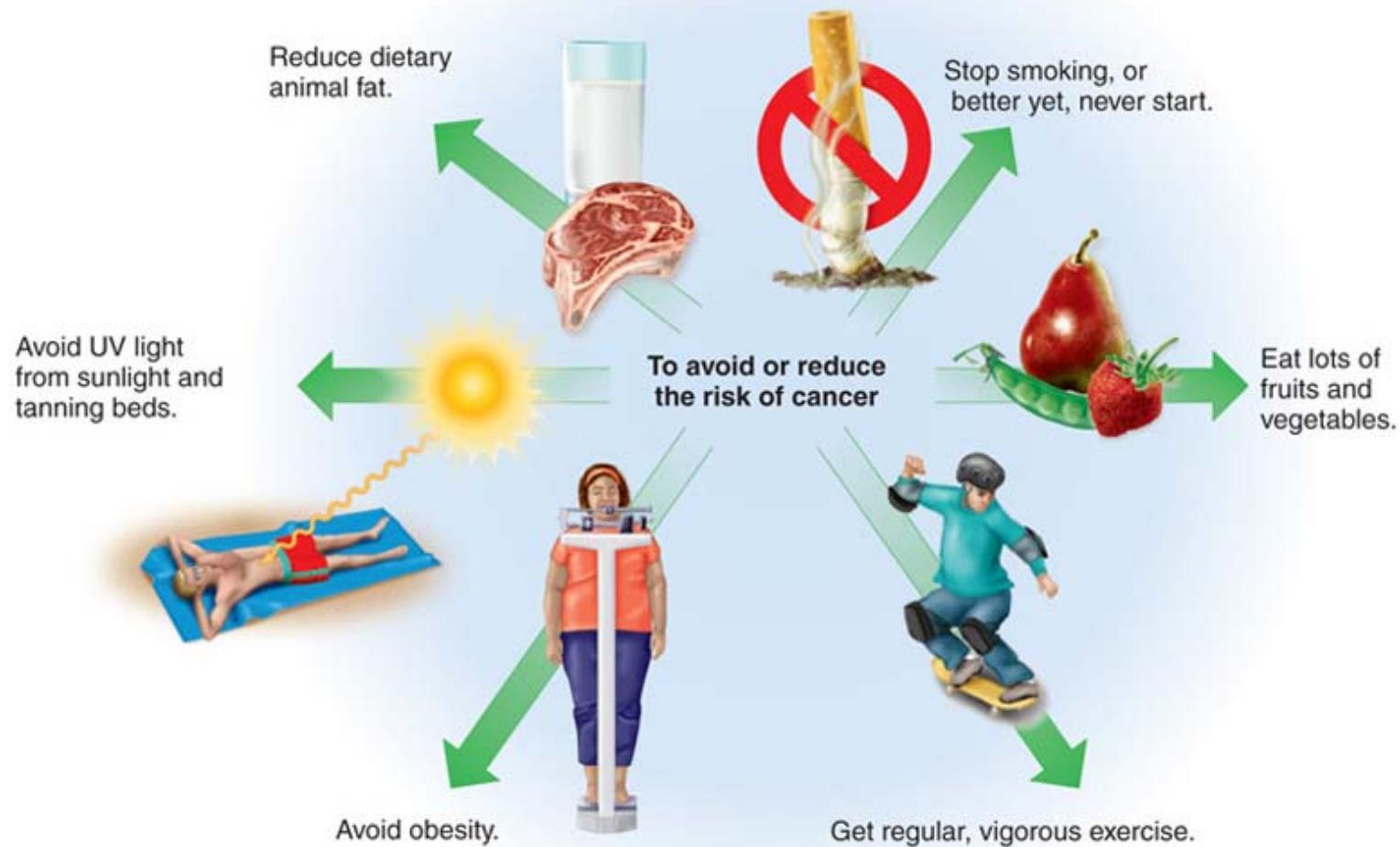
Metastasis is a multi-step procedure



III. Putative causes of tumors and cancers

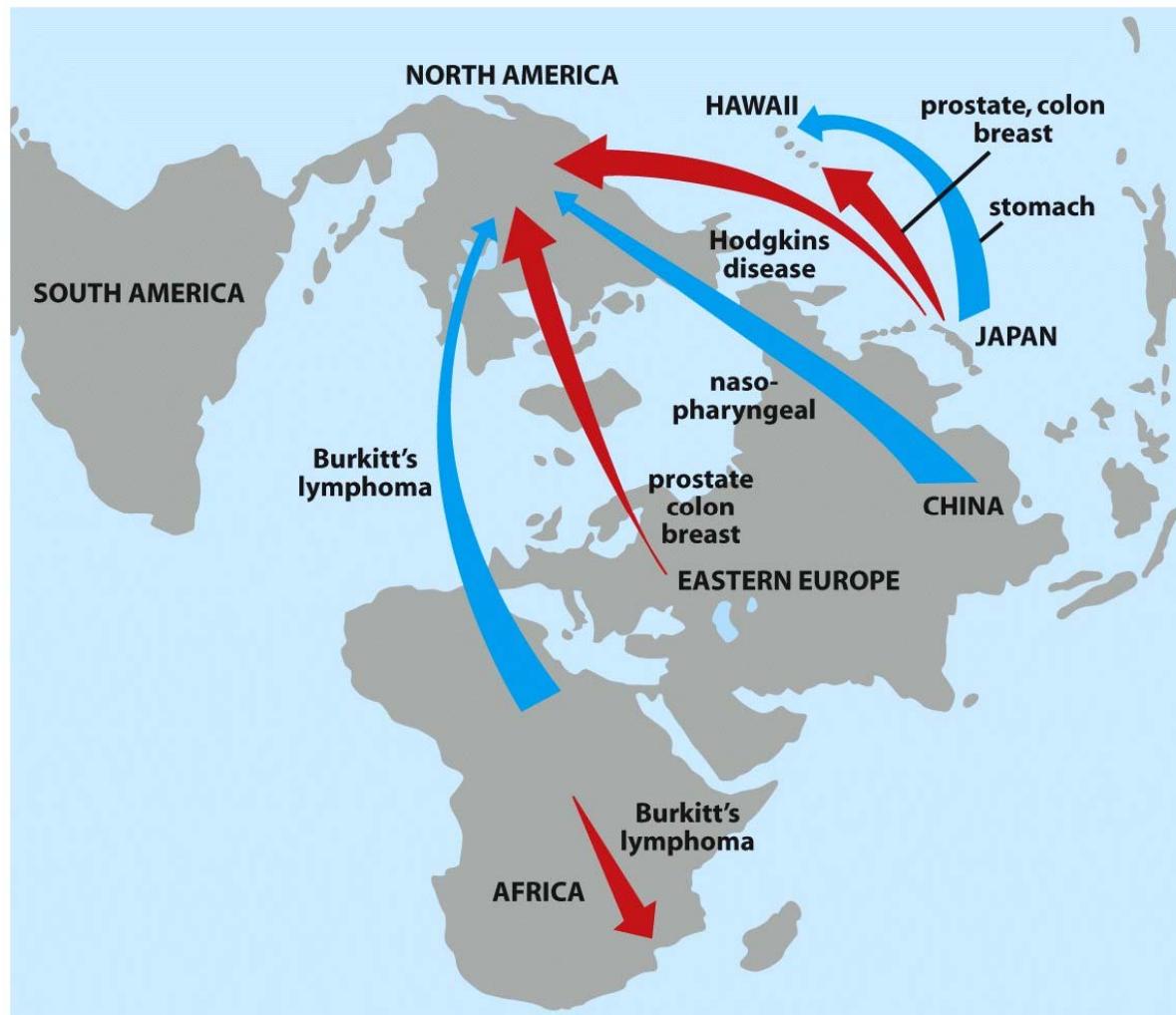
1. Life style
2. Environment
3. Exposure to carcinogens
4. Cancer causing viruses, parasites & bacteria

1. Life style



2. Environment

Cancer incidence is also related to environmental influences...



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, causing DNA damage...

Common carcinogens:

- chemicals:
 - aromatic compounds
 - nitrosamines
 - alkylating agents
 - **whatever binds to DNA (ethidium bromide, midori green? cyber dyes?)**
- Irradiations:
 - X-rays
 - UV

Some very important chemical carcinogens

Aflatoxin B1 (黃曲霉毒素):

- **poisonous fungal carcinogen**, produced by:
 - *Aspergillus flavus* and *Aspergillus parasiticus*, growing in soil, decaying vegetation, hay, and grains.
- Aflatoxins are regularly found in improperly stored staple commodities: **cassava, chili peppers, corn, cotton seed, millet, peanuts, rice, sesame seeds, sorghum, sunflower seeds, tree nuts, wheat, and a variety of spices.**
- **When contaminated food is processed, aflatoxins enter the general food supply where they have been found in both pet and human foods, as well as in feedstocks for agricultural animals.**
- **Animals fed contaminated food can pass aflatoxin transformation products into eggs, milk products, and meat.**

Some very important chemical carcinogens

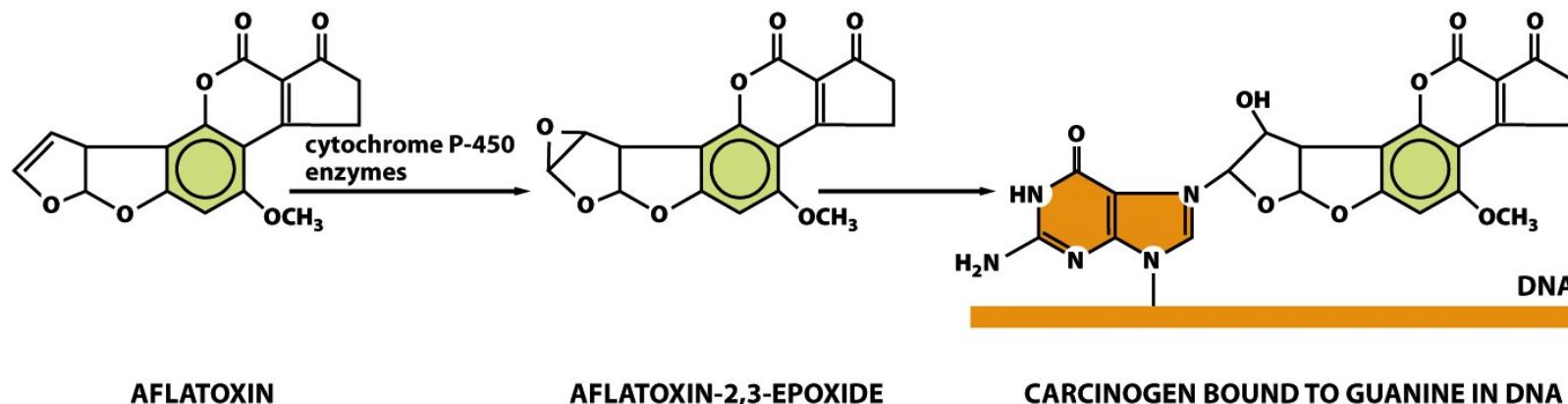
Benzopyrene (苯丙芘):

- polycyclic aromatic hydrocarbon
- result of incomplete combustion of organic matter at temperatures between 300 °C and 600 °C
- The ubiquitous compound can be found in coal tar, tobacco smoke and many foods, especially grilled meats

Some common chemical carcinogen

Aflatoxin B1 (黃曲霉毒素)
Benzopyrene (苯丙芘):

Converted by cytochrome c oxidase
into active carcinogen



Dimethylbenzanthracene (DMBA):

- immunosuppressor and a powerful organ-specific laboratory carcinogen
- DMBA is widely used in many research laboratories studying cancer.
- DMBA serves as a tumor initiator

Some common chemical carcinogen

- **VINYL CHLORIDE:**

liver angiosarcoma

- **BENZENE:**

acute leukemias

- **ARSENIC:**

skin carcinomas, bladder cancer

- **ASBESTOS:**

mesothelioma

- **RADIUM:**

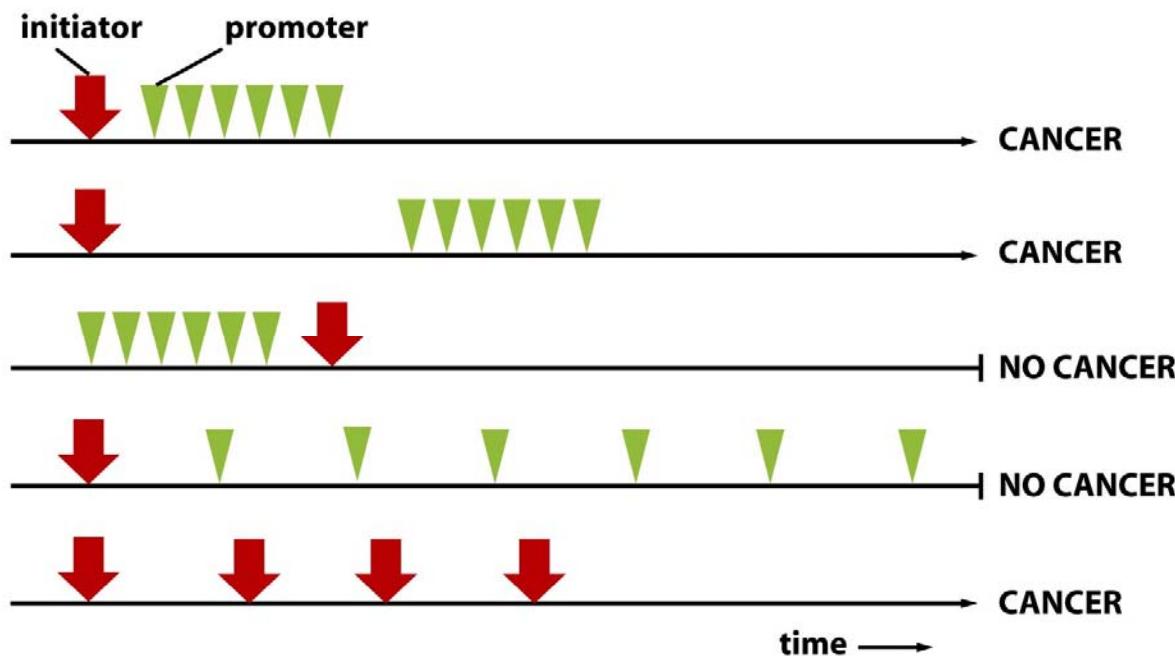
osteosarcoma

Vinyl chloride ($\text{H}_2\text{C}=\text{CHCl}$), also called **vinyl chloride monomer (VCM)** or **chloroethene**. This colorless compound is an important industrial chemical chiefly used to produce the polymer polyvinyl chloride (PVC). About 13 billion kilograms are produced annually.

Cancer onset: Tumor initiator (mutagenic) & tumor promoter (non-mutagenic)

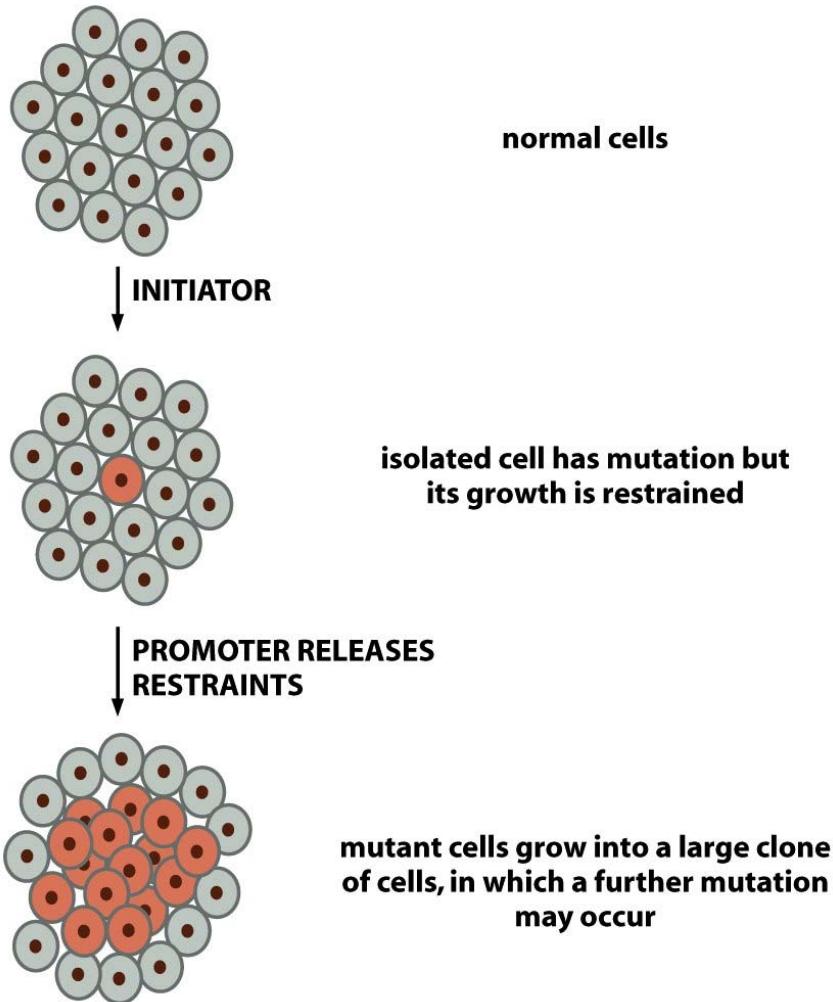
Differences between tumor initiator (mutagenic) and tumor promoter (non-mutagenic)

- **Tumor initiators** causes mutations but do not trigger immediate tumor growth
 - they set the stage for greatly increased incidence of cancer
- **Tumor promoters** do not cause mutations but **stimulate/trigger proliferation** (targeting the cell cycle or, in its easiest case even simple wounding reactions)



Functions for a tumor promoter

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



- The **tumor promotor** creates a **local environment** that **expands the population of mutant cells**.
(triggering/promoting proliferation)
- By this, the tumor promotor **“promotes” the probability of tumor progression** by **“proliferation-triggered” further genetic changes**.
(which would not have occurred without the triggered/occurred proliferation)

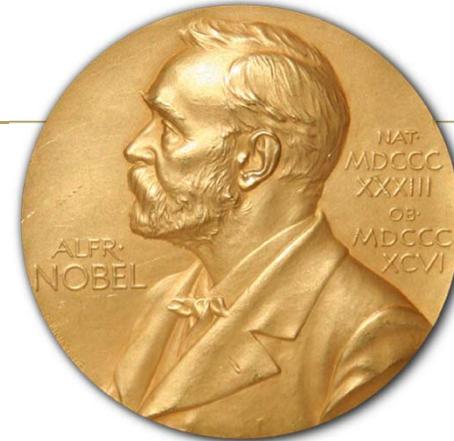
4. The causes of cancer

1.) Cancer can be caused by viruses:



Harald zur Hausen
(born 11 March 1936)
German virologist
Nobel laureate 2008

- HPV (Human papilloma virus)
 - cervical cancer
- MMTV (Mouse mammary tumor virus)
 - murine breast cancer
- HBV (Hepatitis B virus)
 - liver cancer
- MMLV (Moloney murine leukemia virus)
 - leukemia,
- RSV (Rous sarcoma virus)
 - rat sarcoma
- EBV (Epstein-Barr virus)
 - Burkitt's lymphoma
- etc.



Cancer causing viruses

Cancer can be caused by viruses but it is difficult to proof:

- Detection of viruses in cancer patients hints to a relationship:
 - Liver cancer and Hepatitis B virus (**HBV**) infections are widely spread in Africa and Southeast Asia **but cancer occurs exclusively in patients with chronic HBV infections.**
 - **the relationship is difficult to prove since there may be years between the initial viral infection and the development of cancer.**
- Viruses might cause **indirect tumor-promoting effects**
 - **HBV causes chronic inflammation and thus stimulates cell division** (→ tumor promotor, rather than tumor initiator)
- DNA viruses can **carry genes that undermine control of cell division** (Human papilloma virus)
- HIV **destroys the immune system** and **allows for secondary infection** (e.g. the human herpes virus 8 (**HHV-8**) that has direct carcinogenic action)

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.

The causes of cancer

2.) Cancer can also be caused by parasites

Parasites:

- *Schistosoma haematobium* (blood fluke), a parasitic flatworm
 - Chronic infection triggers bladder cancer.
Viruses might cause **indirect tumor-promoting** effects
 - HBV causes chronic inflammation and thus stimulates cell division
(→ tumor promotor, rather than tumor initiator)



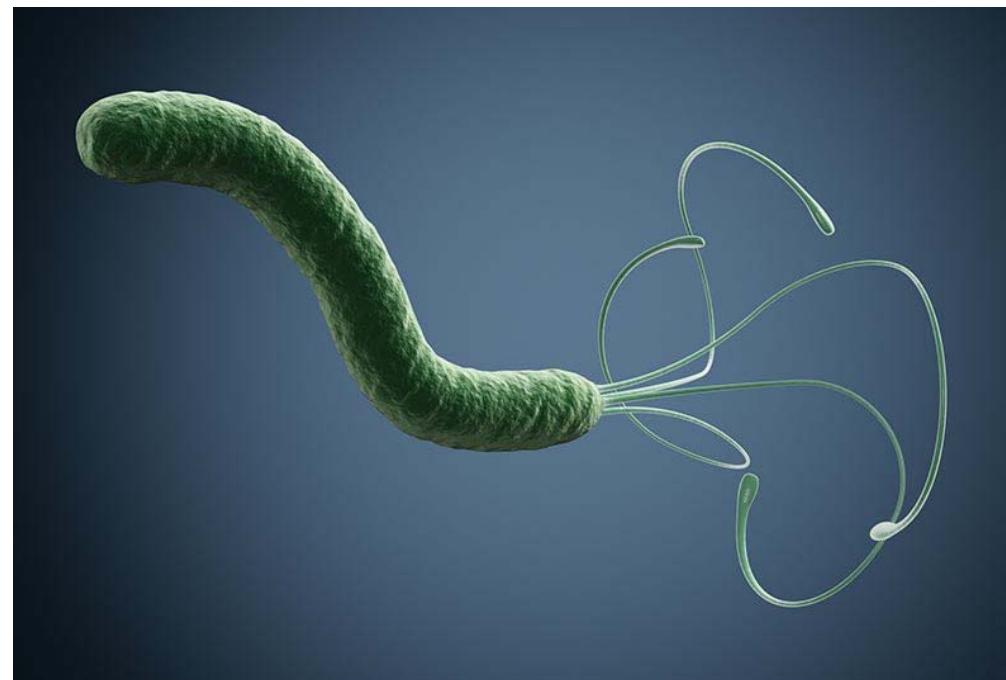
The causes of cancer

3.) Cancer can also be caused by bacteria

Bacteria:

- *Helicobacter pylori*

- causes ulcers and appears to be the major cause of stomach cancer



Spiral-shaped *H. pylori* is the only bacteria known to colonize the human stomach. An estimated 50 percent of humans harbor *H. pylori* in their gut, but only some develop ulcers or stomach cancer. Photo by lucadp/iStock

Helicobacter pylori might cause gastric cancer



Barry J. Marshall and J. Robin Warren



The Nobel Prize in
Physiology or Medicine for 2005
jointly to
Barry J. Marshall and J. Robin Warren
for their discovery of "the bacterium
Helicobacter pylori and its role in
gastritis and peptic ulcer disease"

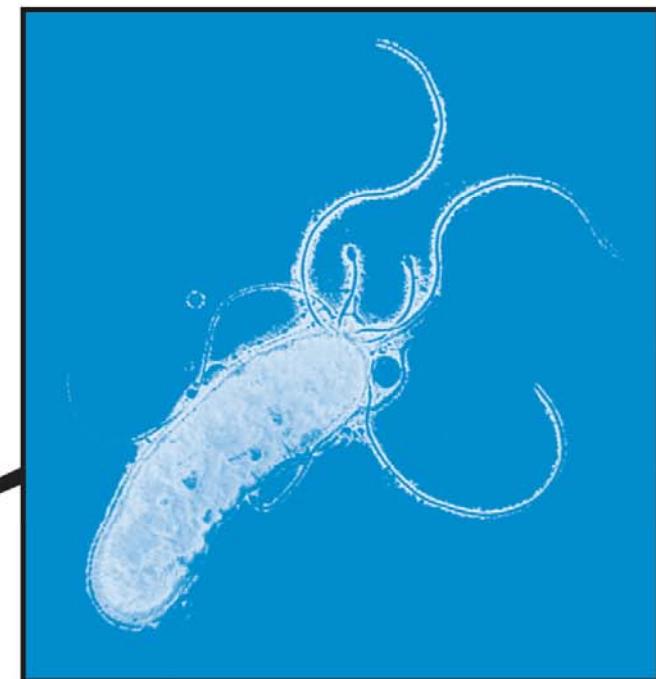
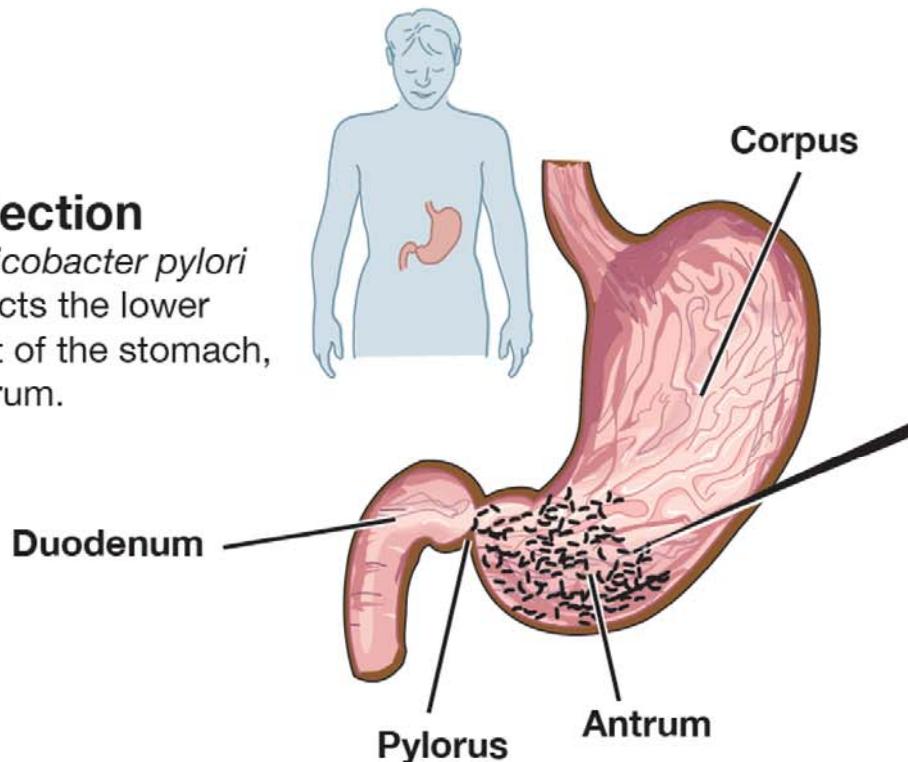
Helicobacter pylori might cause gastric cancer

Helicobacter pylori

— the bacterium causing peptic ulcer disease

Infection

Helicobacter pylori infects the lower part of the stomach, antrum.

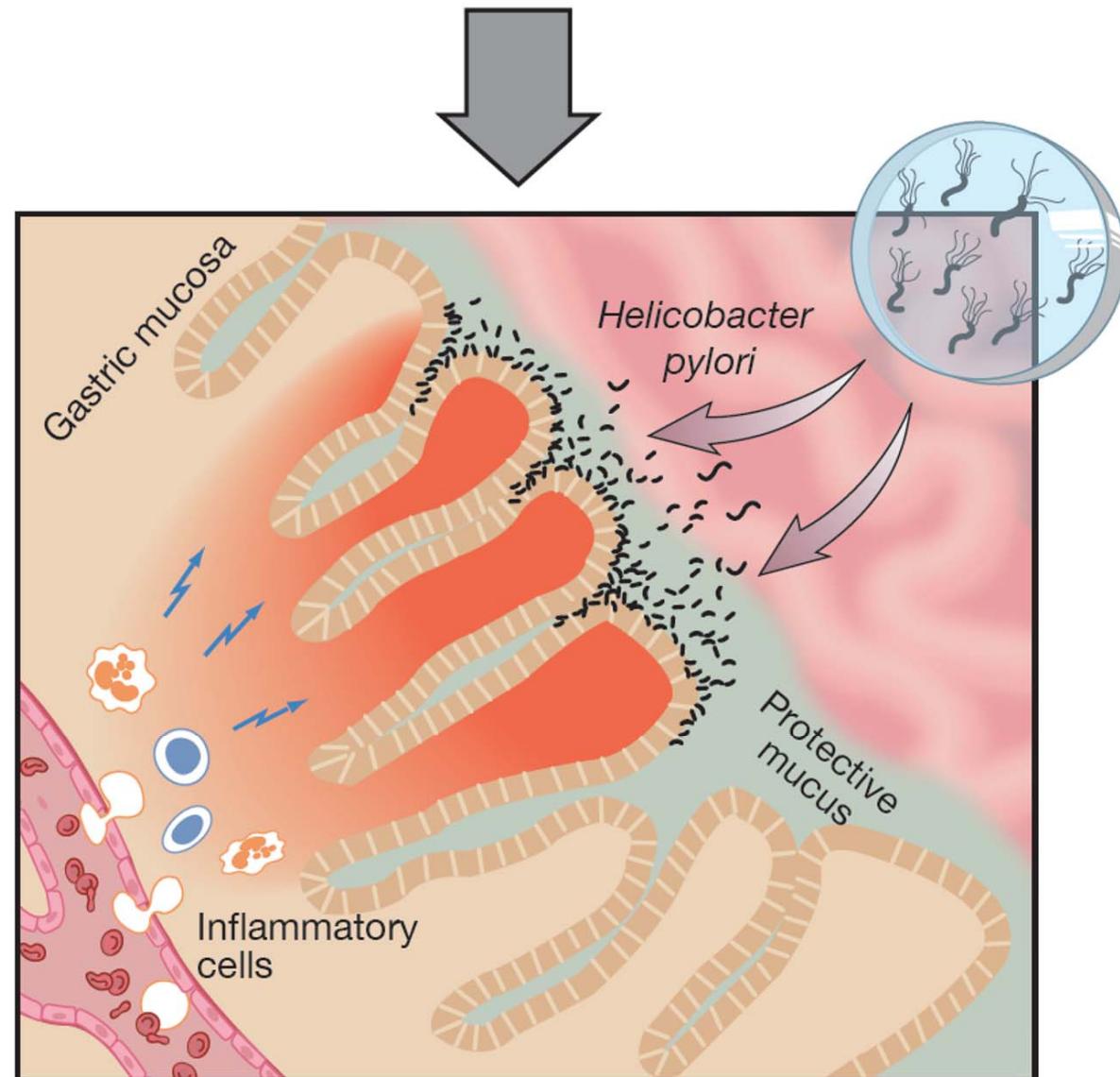


Helicobacter pylori

Helicobacter pylori might cause gastric cancer

Inflammation

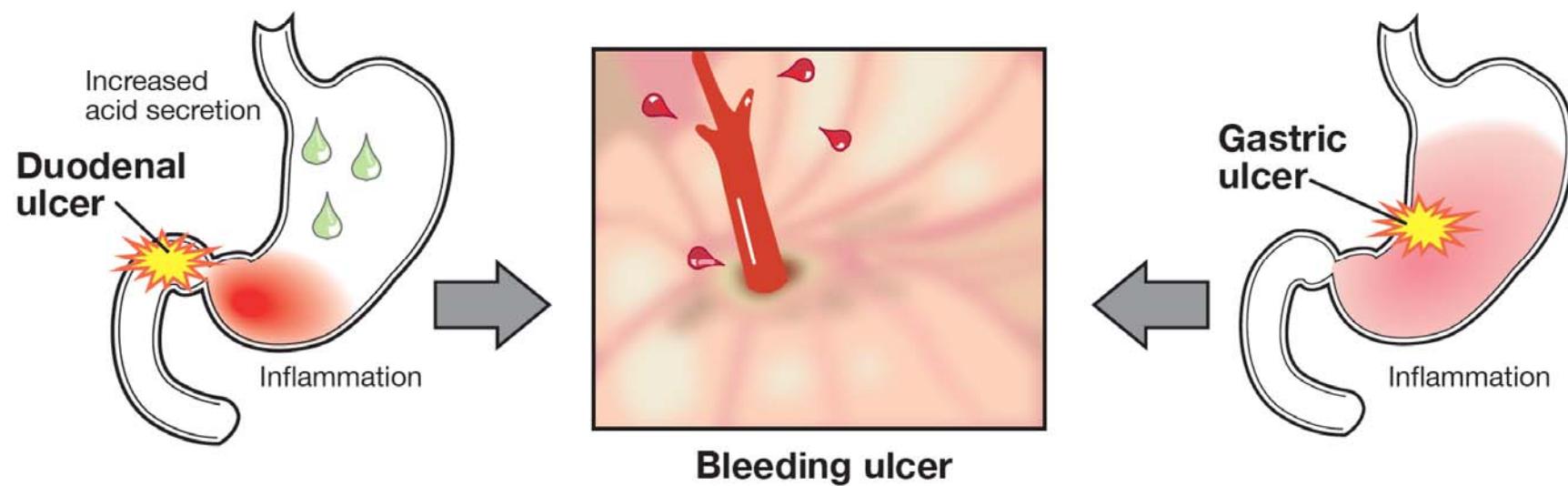
Helicobacter pylori causes inflammation of the gastric mucosa (gastritis). This is often asymptomatic.



Helicobacter pylori---gastric cancer

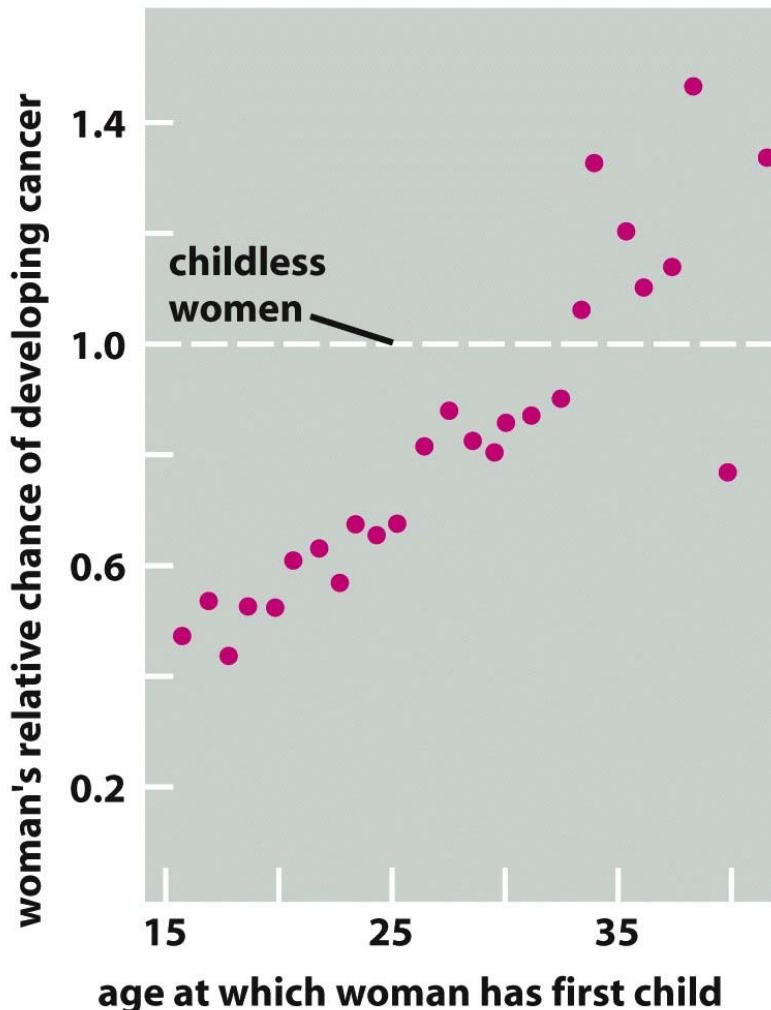
Ulcer

Gastric inflammation may lead to duodenal or gastric ulcer. Severe complications include bleeding ulcer and perforated ulcer.



Other factors: reproductive hormones might also trigger cancer

Effects of childbearing on the risk of breast cancer



The reason for this is not yet understood:
Interpretation of the data:

Prolonged exposure to reproductive hormones enhances the risk for developing cancer.

Assumption:

Here it is also assumed that the first full-term pregnancy results in final differentiation of the cells.

This final differentiation alters cellular responses to the hormones.

IV. Cancer critical genes

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

How were cancer critical genes discovered?

Discovery of sarcoma (Src) genes

First things first: The egg or the chicken?

This time, it started with the chicken

- Peyton Rous: Sarcoma induction in chicken by a cell-free tumor filtrate
(→ discovery of the **Rous sarcoma virus**, RSV)



Later, Rous discovered that sarcoma virus DNA can induce sarcoma formation

How were cancer critical genes discovered?

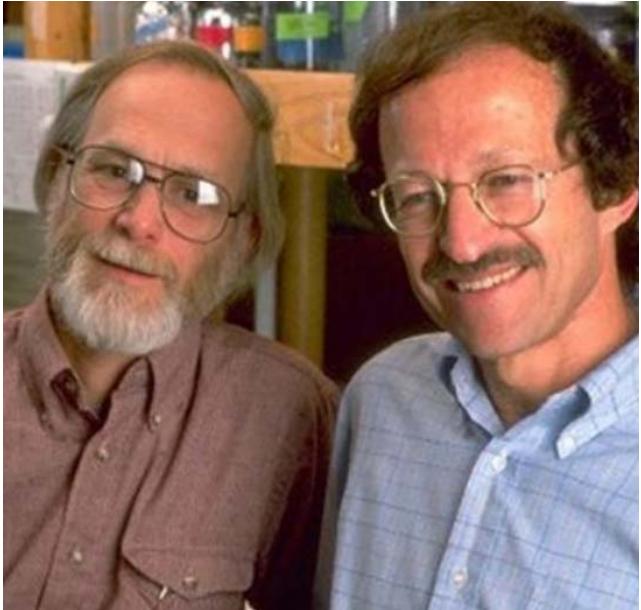
The sarcoma (**Src**) genes were the first discovered retroviral oncogenes

First things first: The egg or the chicken?

This time, it started with the chicken

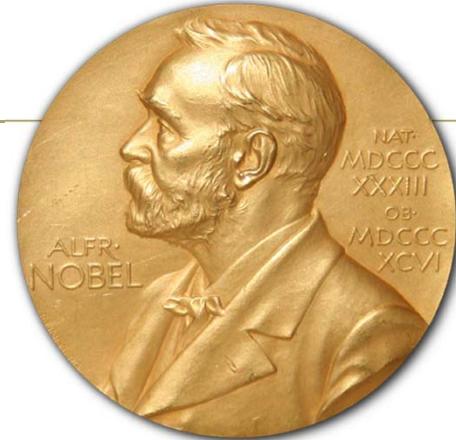
- Peyton Rous: Sarcoma induction in chicken by a cell-free tumor filtrate
(→ discovery of the **Rous sarcoma virus**, RSV)

Cellular origin of retroviral oncogenes



J.M. Bishop & H.E. Varmus

Nobel laureate 1989



Discovery of "the cellular origin of retroviral oncogenes".

Summary

The discovery awarded with this year's Nobel Prize in Physiology or Medicine concerns the **identification of a large family of genes which control the normal growth and division of cells**. Disturbances in one or some of these so-called *oncogenes* (Gk ónco(s) bulk, mass) can lead to transformation of a normal cell into a tumor cell and result in cancer.

Alteration of “cancer-critical genes” influence cancer development

Cancer-critical genes: proto-oncogenes vs. tumor suppressors

Proto-oncogenes

- Genes in which a **gain-of-function** mutations contributes towards cancer development
- Their mutant, **overactive** or **overexpressed** forms are called **oncogenes**

Tumor suppressor genes

- Genes in which a **loss-of-function** mutations contributes towards cancer development
- Their gene products suppress the occurrence of cancer

Examples:

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

Oncogenes and tumor suppressors: how to search?

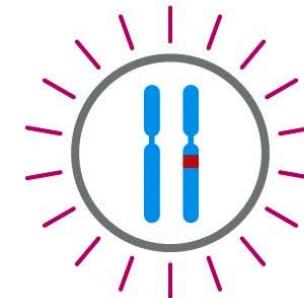
The same result but two different ways: gain of function vs. loss of function

Dominant, growth-promoting effect: oncogenes can be identified upon addition

(A) overactivity mutation (gain of function)



single mutation event
creates oncogene



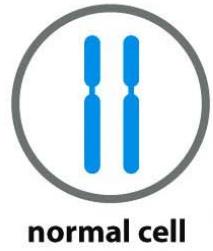
activating mutation
enables oncogene to
promote cell transformation

What is added?
(Src is added, it's
an oncogene)

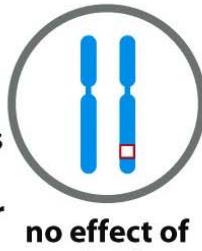
cells
en route to
cancer

Suppressors are recessive, growth-promoting
inhibition occurs if **both** alleles are affected

(B) underactivity mutation (loss of function)

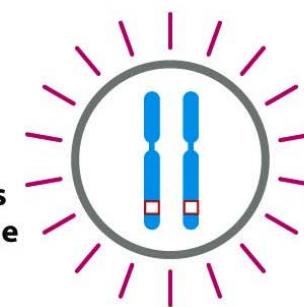


mutation
event
inactivates
tumor
suppressor
gene



no effect of
mutation in one
gene copy

second
mutation
event
inactivates
second gene
copy



two inactivating mutations
functionally eliminate the
tumor suppressor gene,
promoting cell transformation

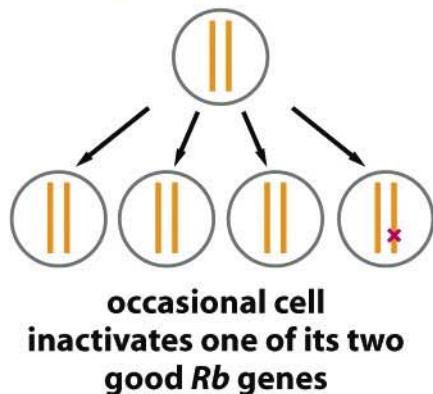
What is lost?
(Src can't be a
suppressor!)

Tumor suppressors: How to identify a gene that is not there?

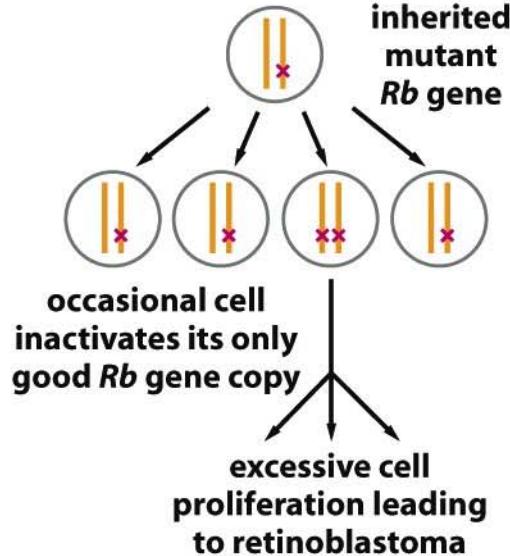
Rb (retinoblastoma) gene identification: infected individual has a deletion of a certain band in his chromosome 13.

Both copies of the Rb gene need to be defective to confer cancer phenotype

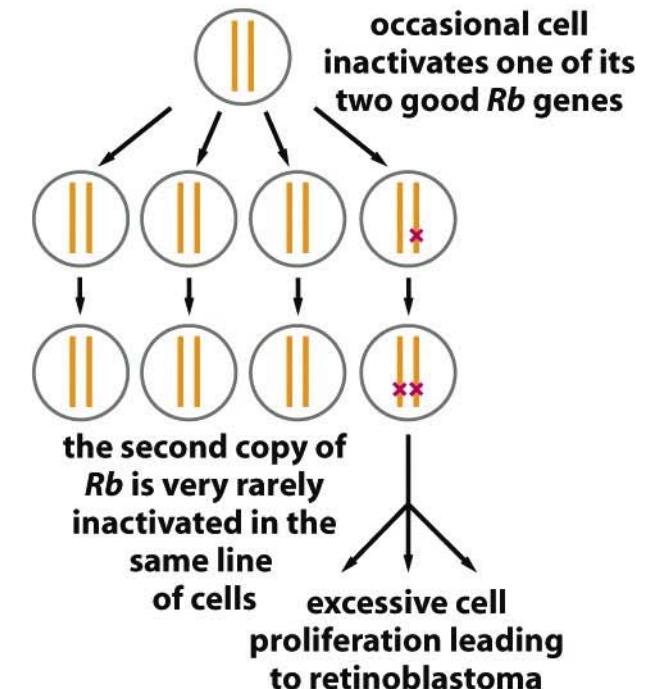
NORMAL, HEALTHY INDIVIDUAL



HEREDITARY RETINOBLASTOMA



NONHEREDITARY RETINOBLASTOMA



RESULT: NO TUMOR

RESULT: MOST PEOPLE WITH INHERITED MUTATION DEVELOP MULTIPLE TUMORS IN BOTH EYES

RESULT: ONLY ABOUT 1 IN 30,000 NORMAL PEOPLE DEVELOP ONE TUMOR IN ONE EYE

Tumor suppressors: How to identify a gene that is not there?

Discovery of the first tumor suppressor: the **retinoblastoma (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
- 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

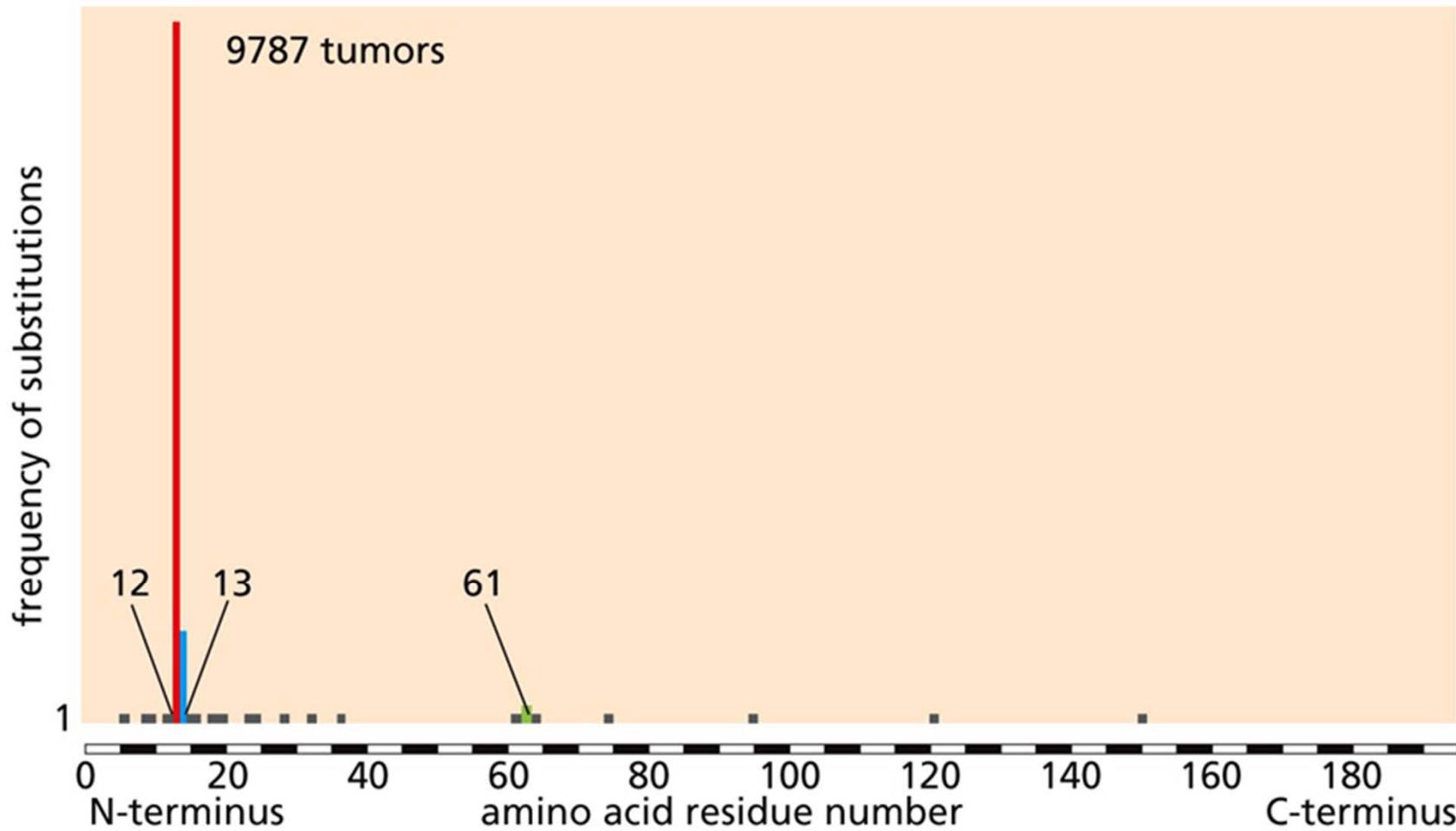


Figure 4.10 The Biology of Cancer (© Garland Science 2014)

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

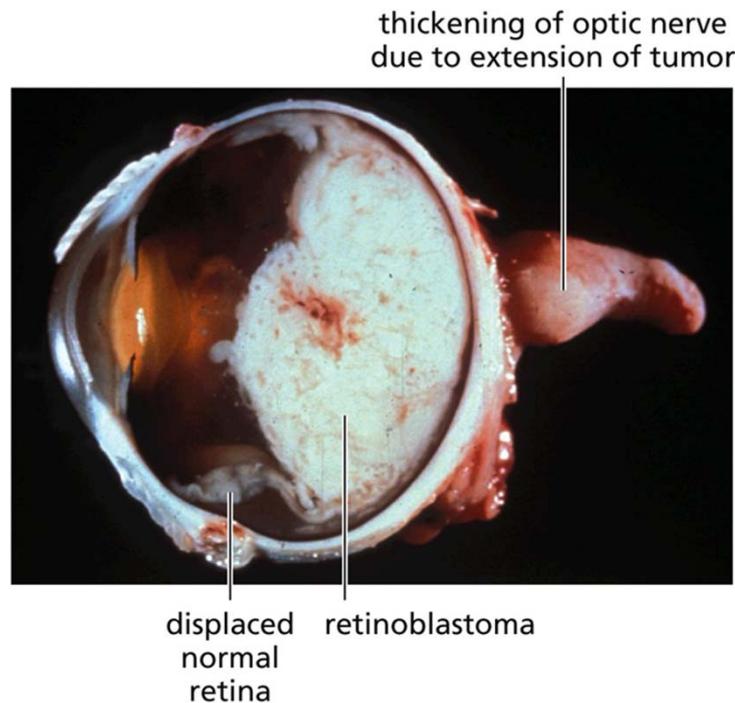


Figure 7.3c The Biology of Cancer (© Garland Science 2014)

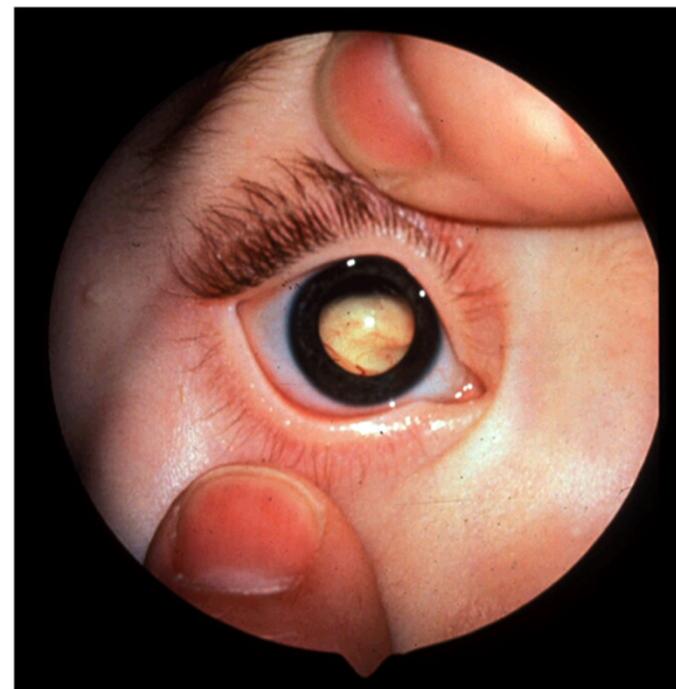


Figure 7.3d The Biology of Cancer (© Garland Science 2014)

Rb and cell cycle control

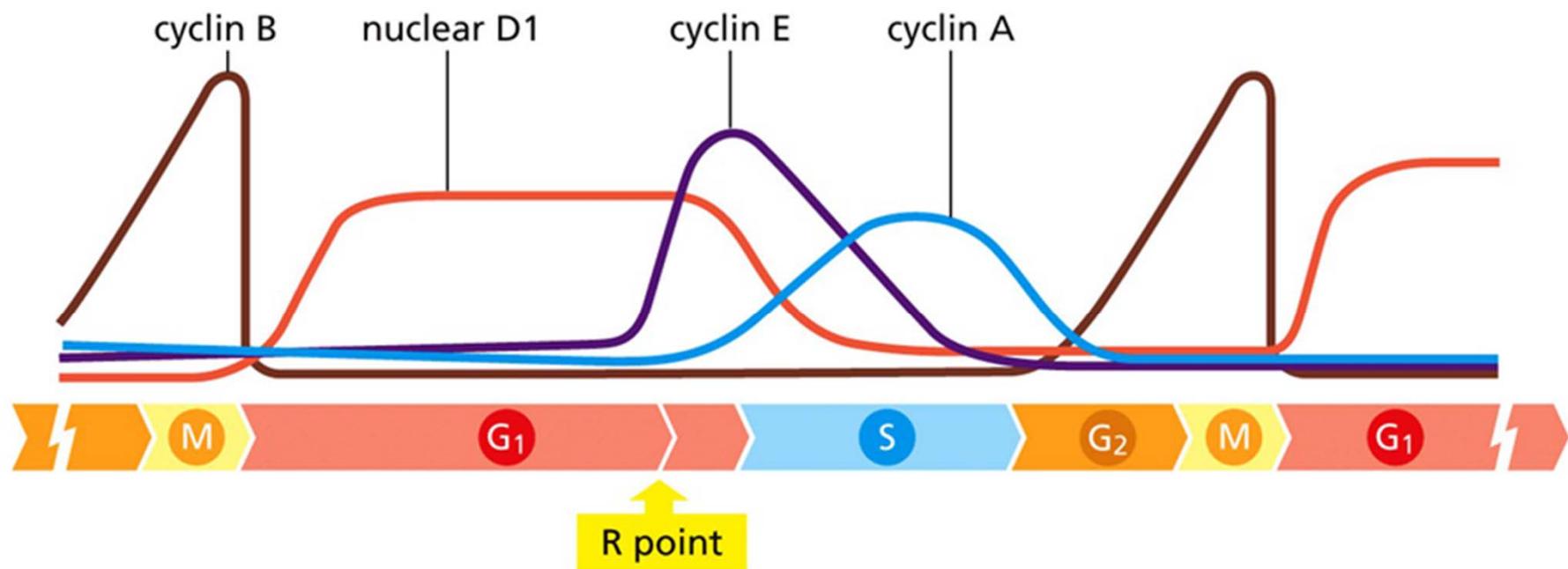


Figure 8.10 The Biology of Cancer (© Garland Science 2014)

Phosphorylation of Rb promotes cyclin E/cdk activity

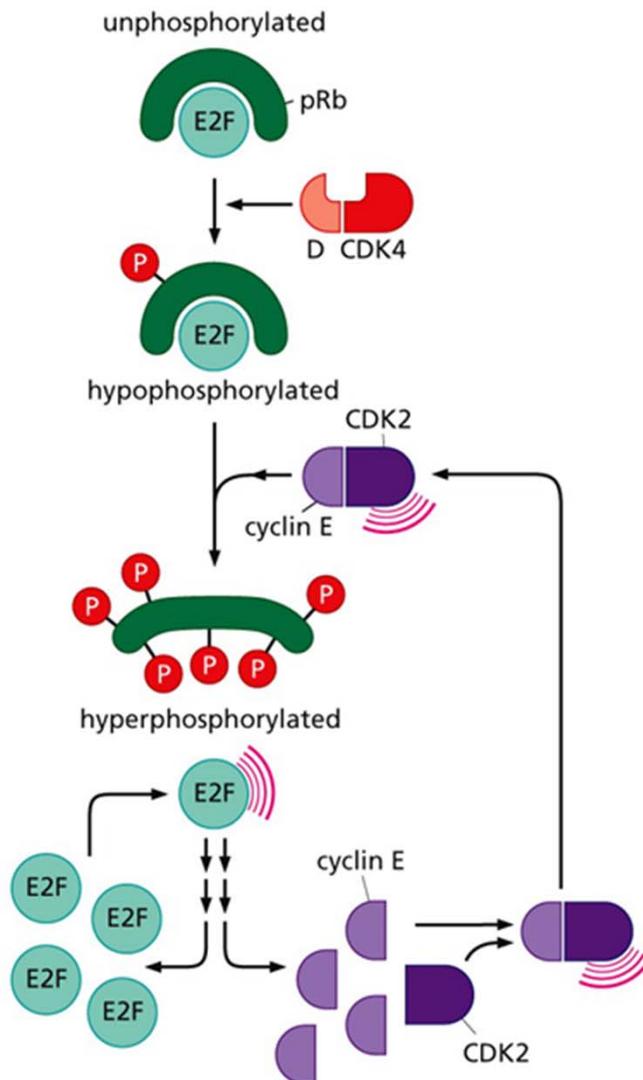


Figure 8.25a The Biology of Cancer (© Garland Science 2014)

Mutation of p53 in human cancers

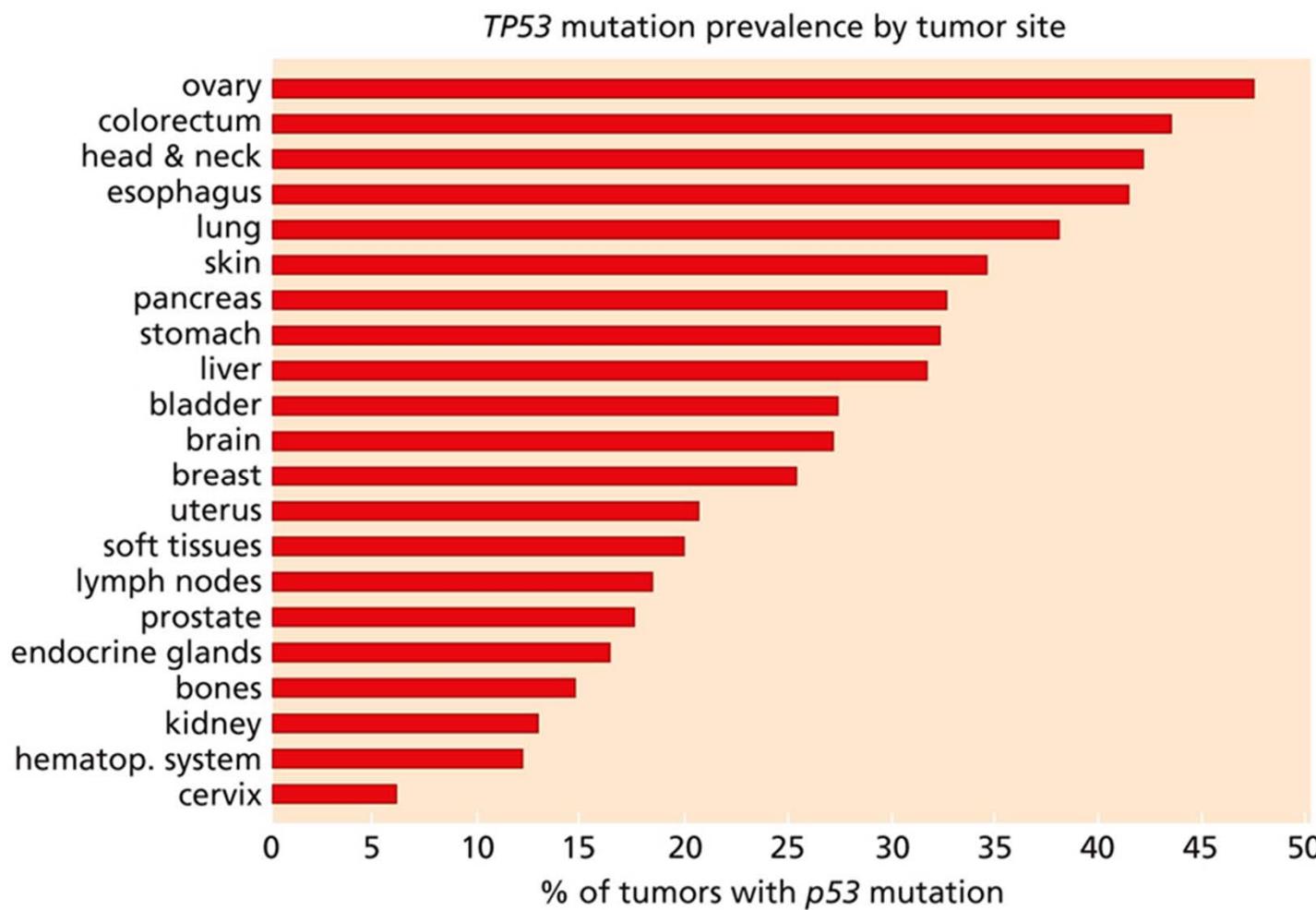


Figure 9.4 The Biology of Cancer (© Garland Science 2014)

Models of action of p53 tumor suppressor

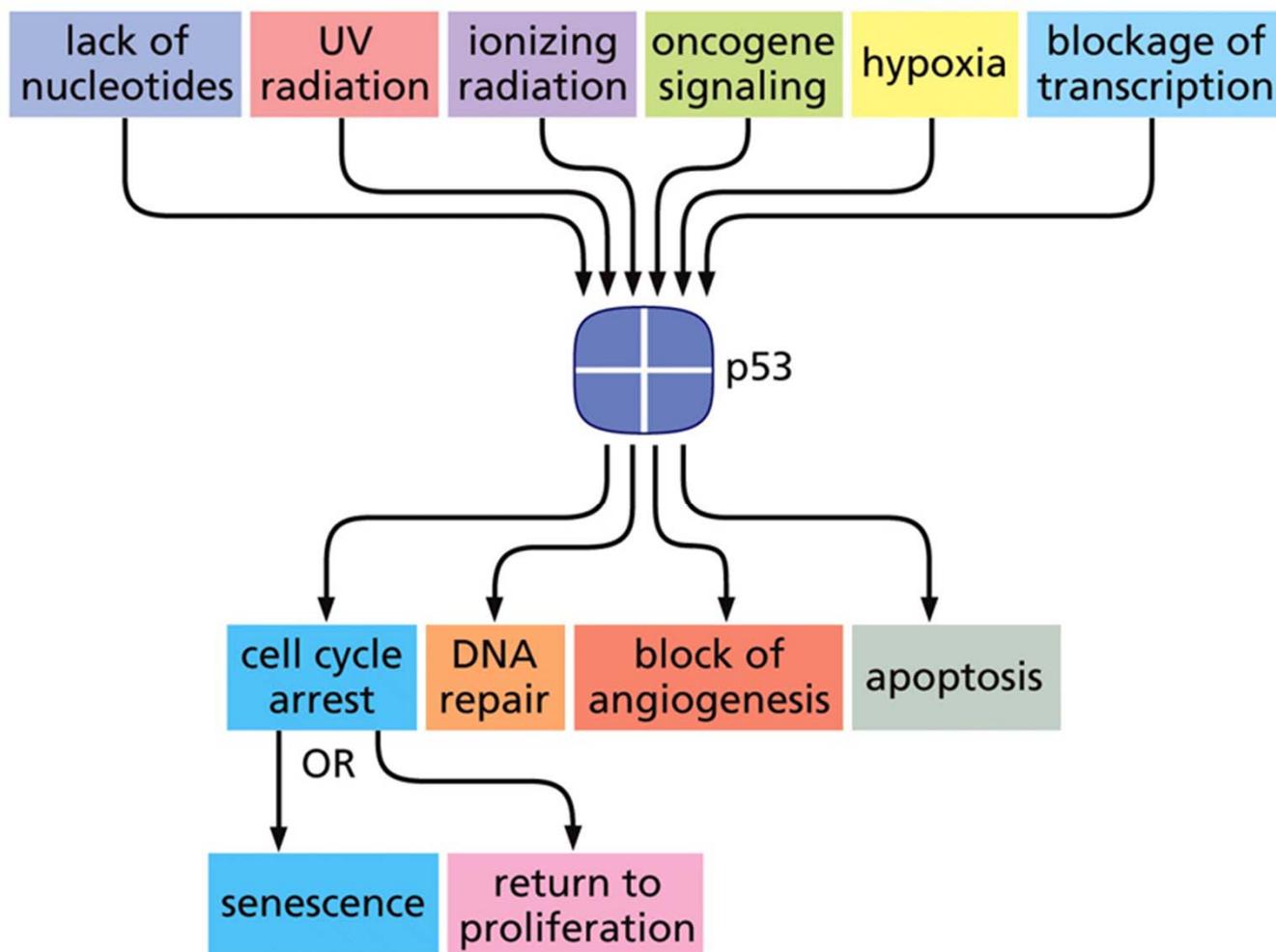
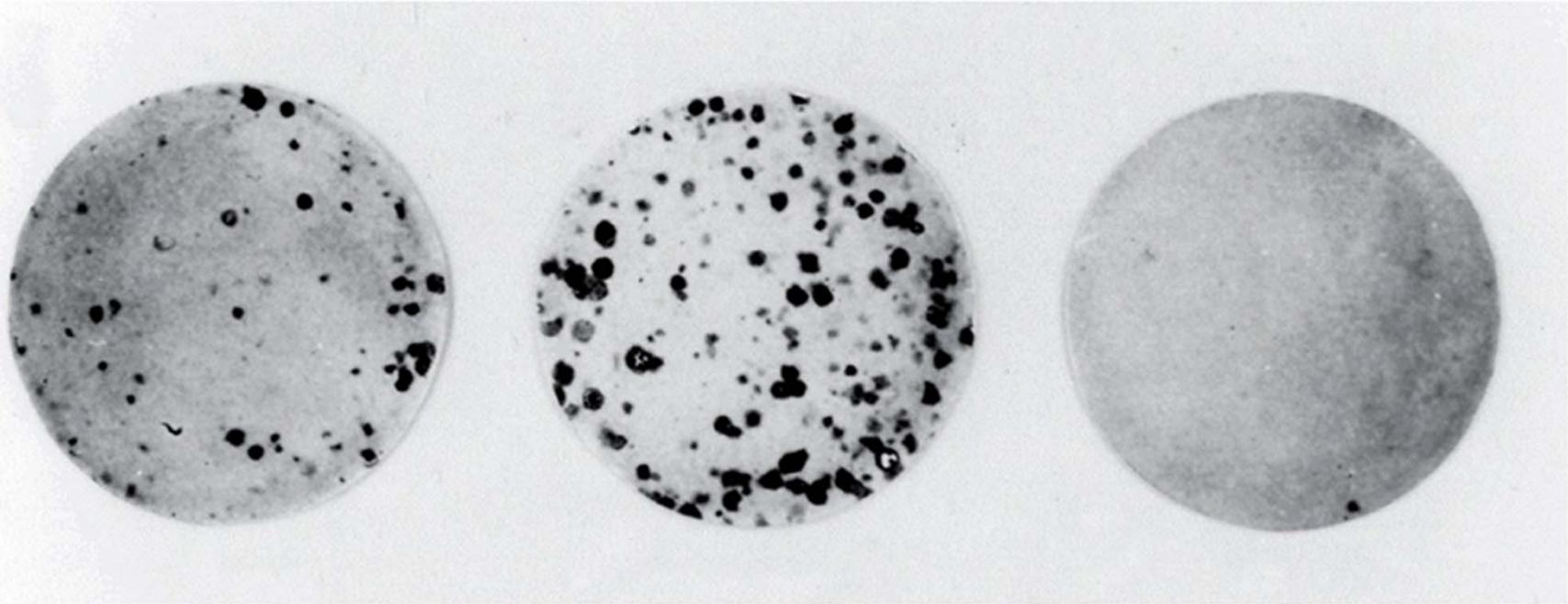


Figure 9.8 The Biology of Cancer (© Garland Science 2014)

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)

Mode of action for HPV

QUIESCENT NORMAL CELL

Rb protein binds cell proliferation factor



inactive cell proliferation factor (gene regulatory protein)

active p53 protein provides safety brake on cell proliferation



P21 TRANSCRIPTION

CELL PROLIFERATION BLOCKED

VIRUS INFECTION PRODUCES E6 AND E7

active cell proliferation factor



viral protein E7

CYCLIN E TRANSCRIPTION

inactive p53

viral protein E6



CELL PROLIFERATION ACTIVATED BY DNA VIRUS

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

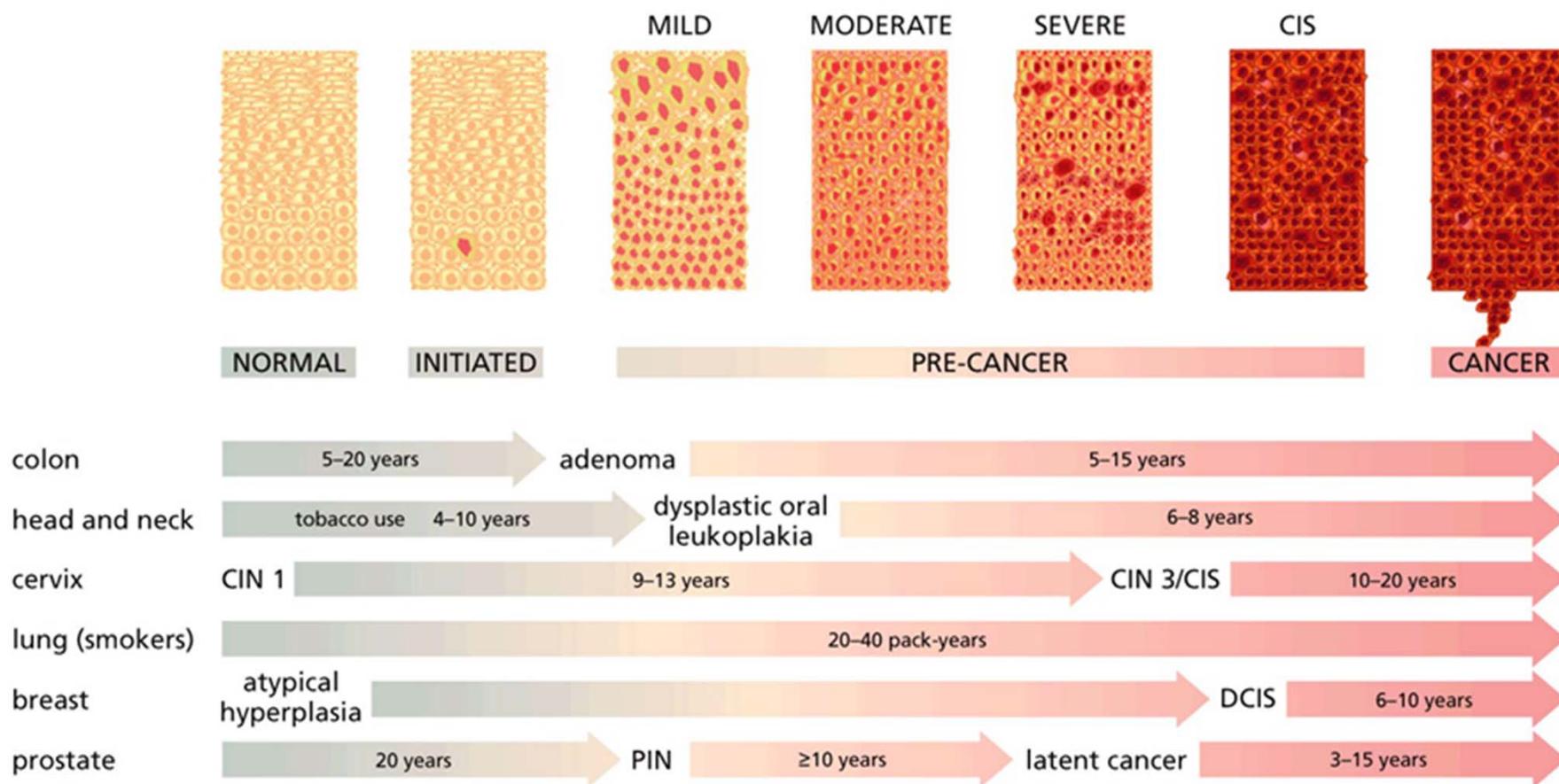


Figure 11.8a The Biology of Cancer (© Garland Science 2014)

Darwinian evolution and clonal succession

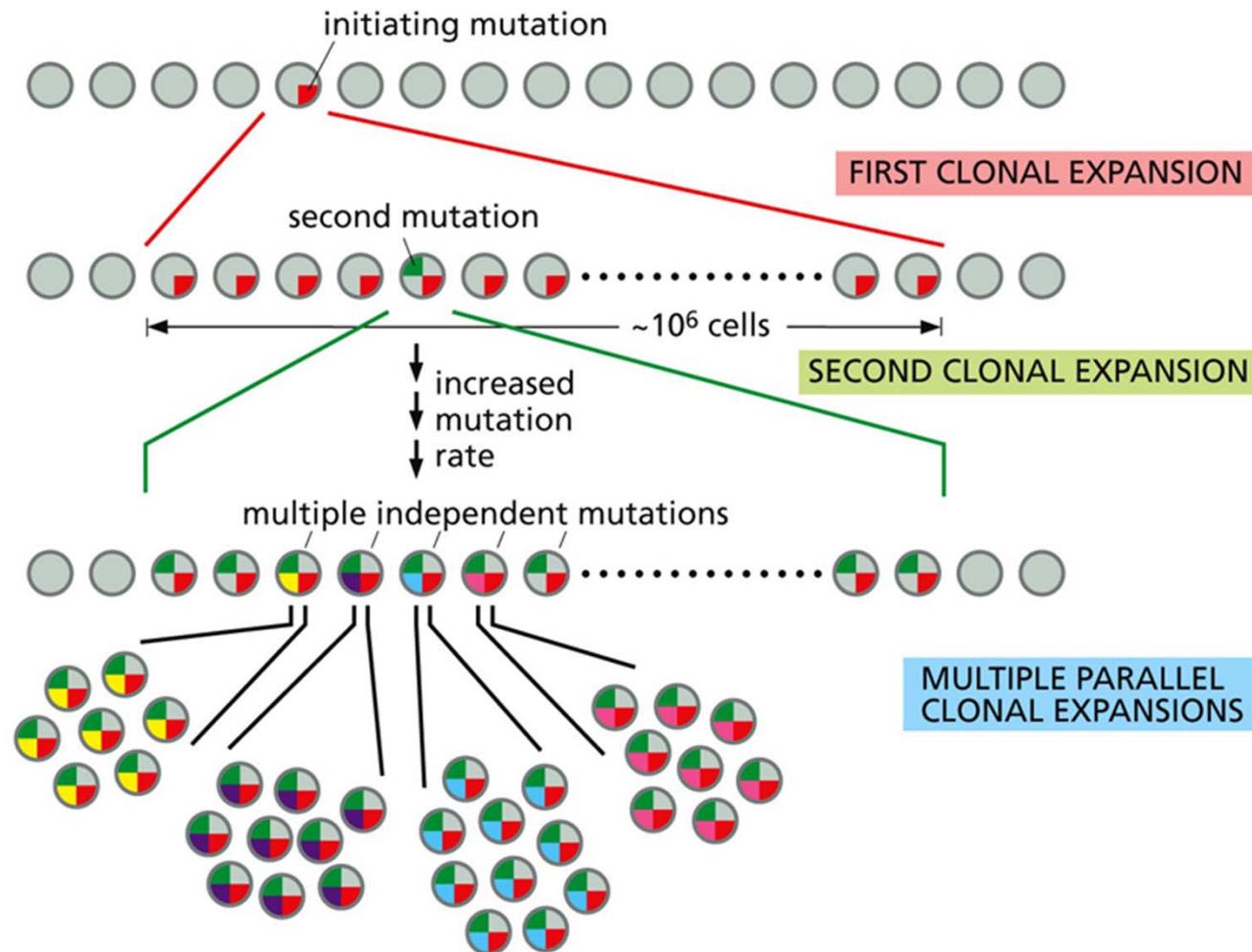
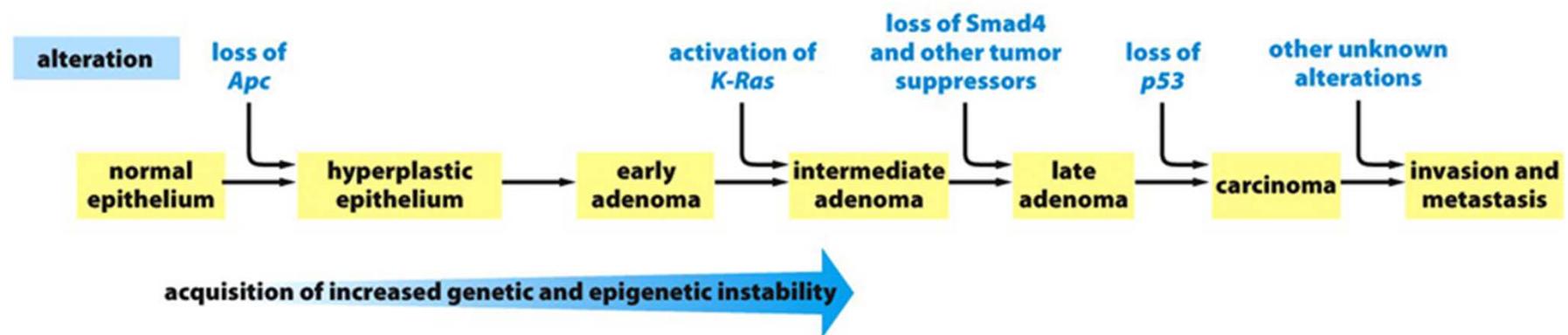


Figure 11.20a The Biology of Cancer (© Garland Science 2014)

Genetic changes underlying the development of colorectal carcinoma



Diversification within a tumor

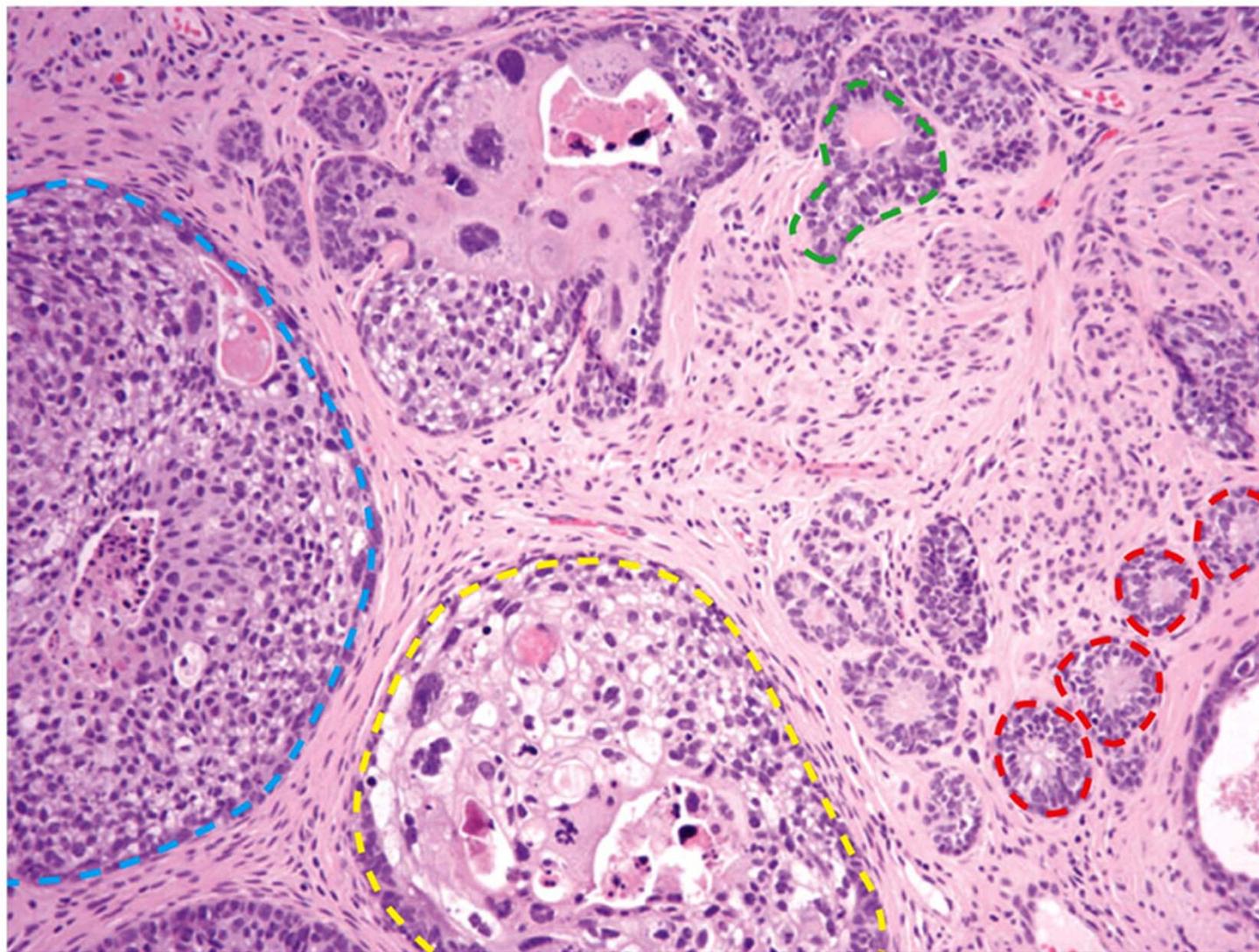


Figure 11.21a The Biology of Cancer (© Garland Science 2014)

VI. Cancer stem cells

Take a tumor mass, make single cell suspension



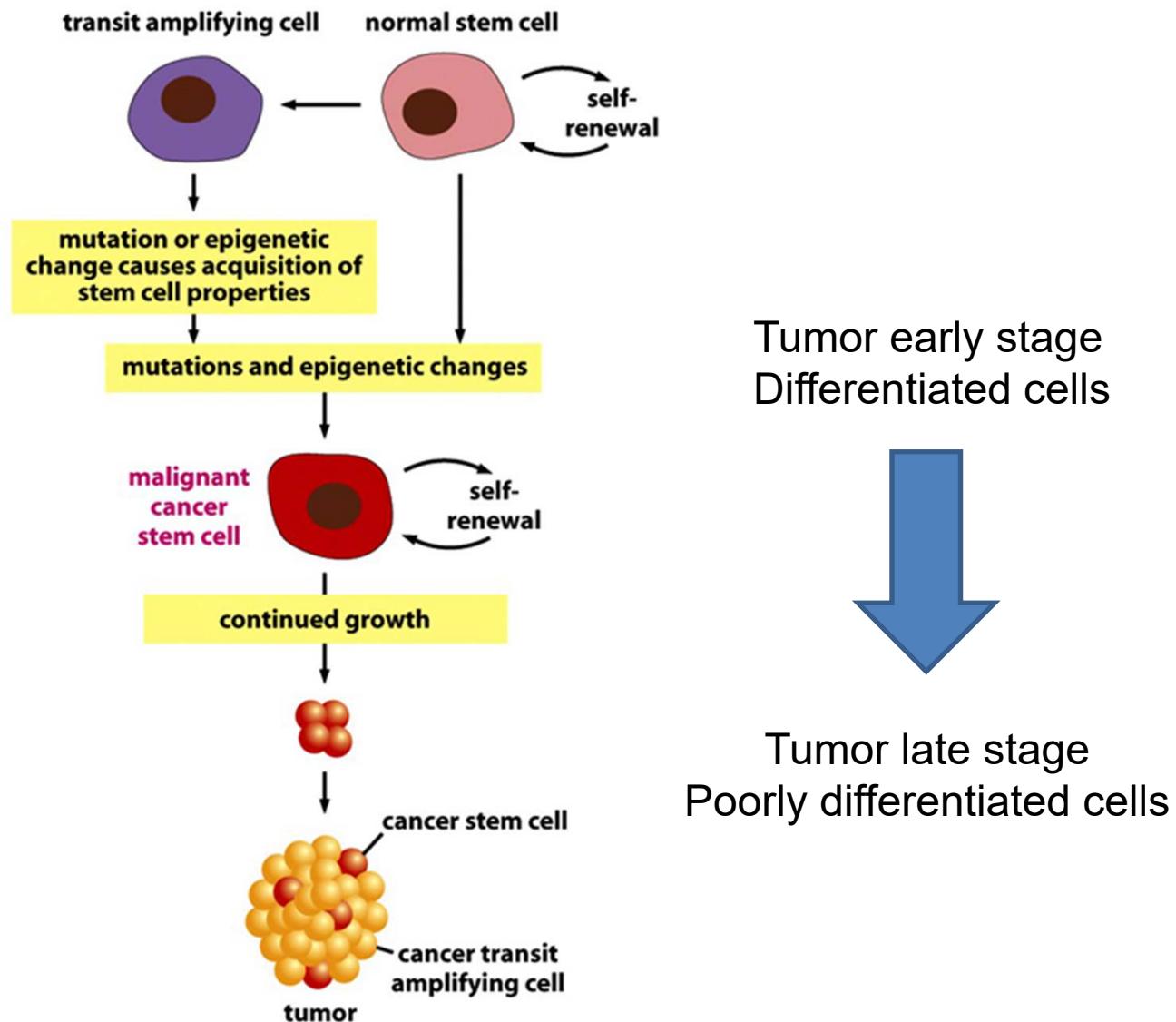
Inject single cell into immunodeficiency mice to induce tumor formation



<<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.

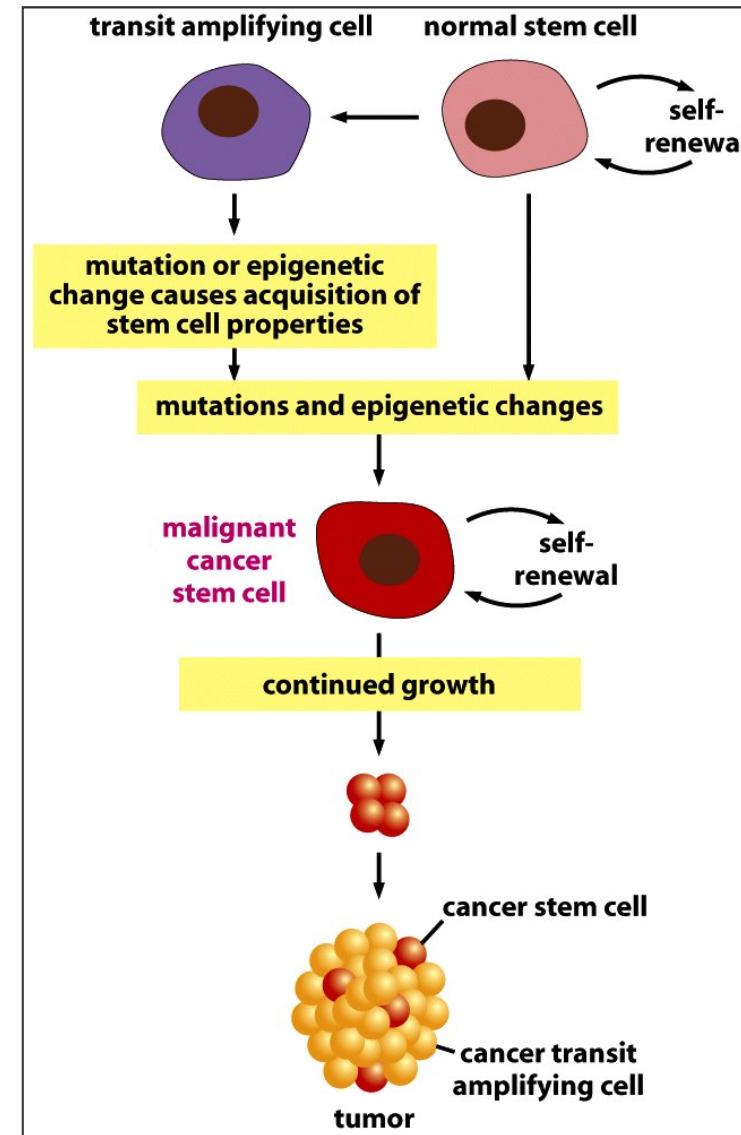
Cancers **may** arise from cancer stem cells



Cancers may arise from cancer stem cells

What is a cancer stem cell?

- **Cancer stem cells can self-renew** to produce additional malignant stem cells **and** to produce non-tumorigenic cells like “transit amplifying cells”
- Cancer stem cells can arise from “normal” stem cells (after mutagenesis) or from more differentiated cells (after mutagenesis/epigenetic changes) to obtain stem cell properties



VII. Tumor metastasis

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

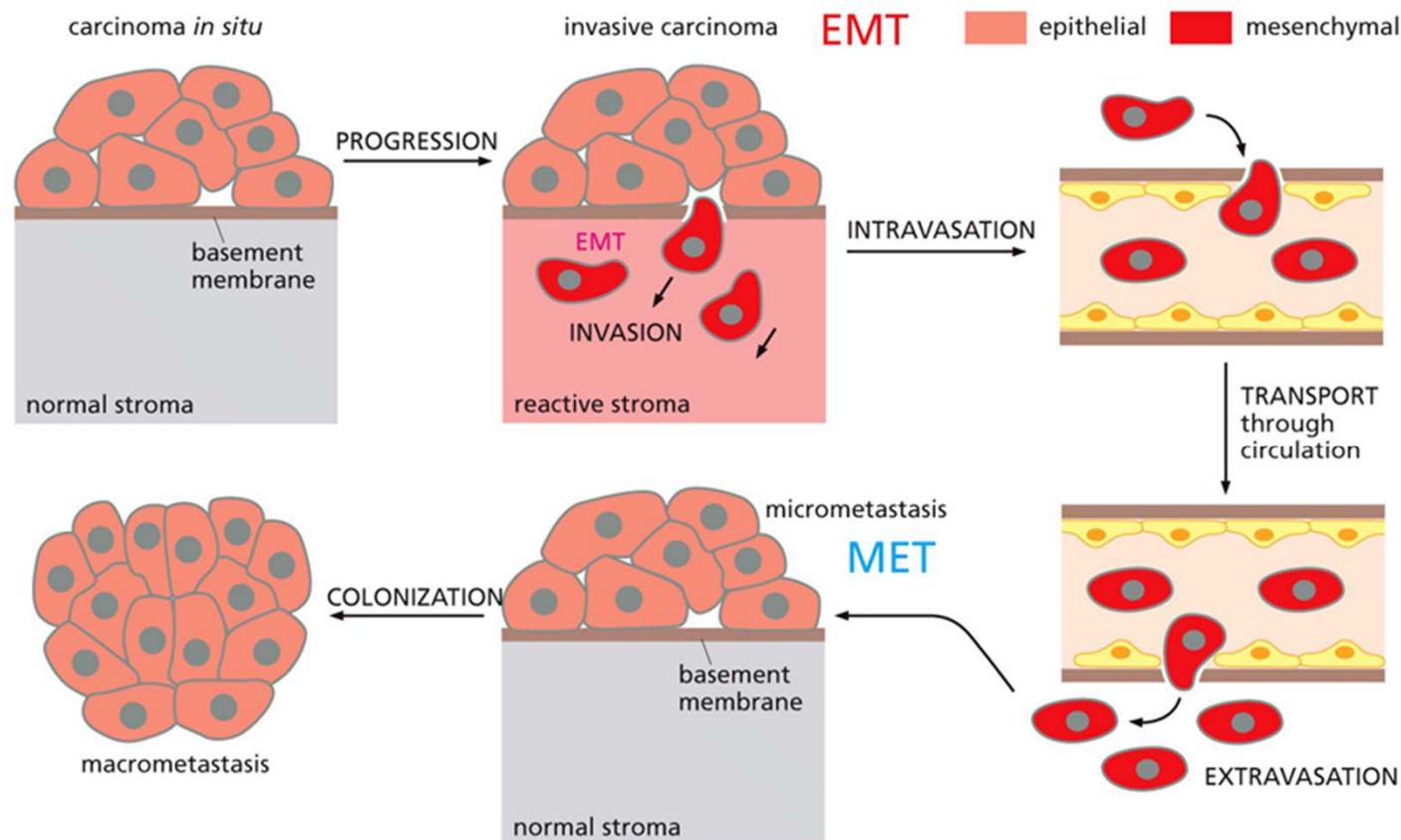


Figure 14.18b The Biology of Cancer (© Garland Science 2014)

Epithelial-mesenchymal transition is important in metastasis

EMT promoting transcription factors promotes metastasis

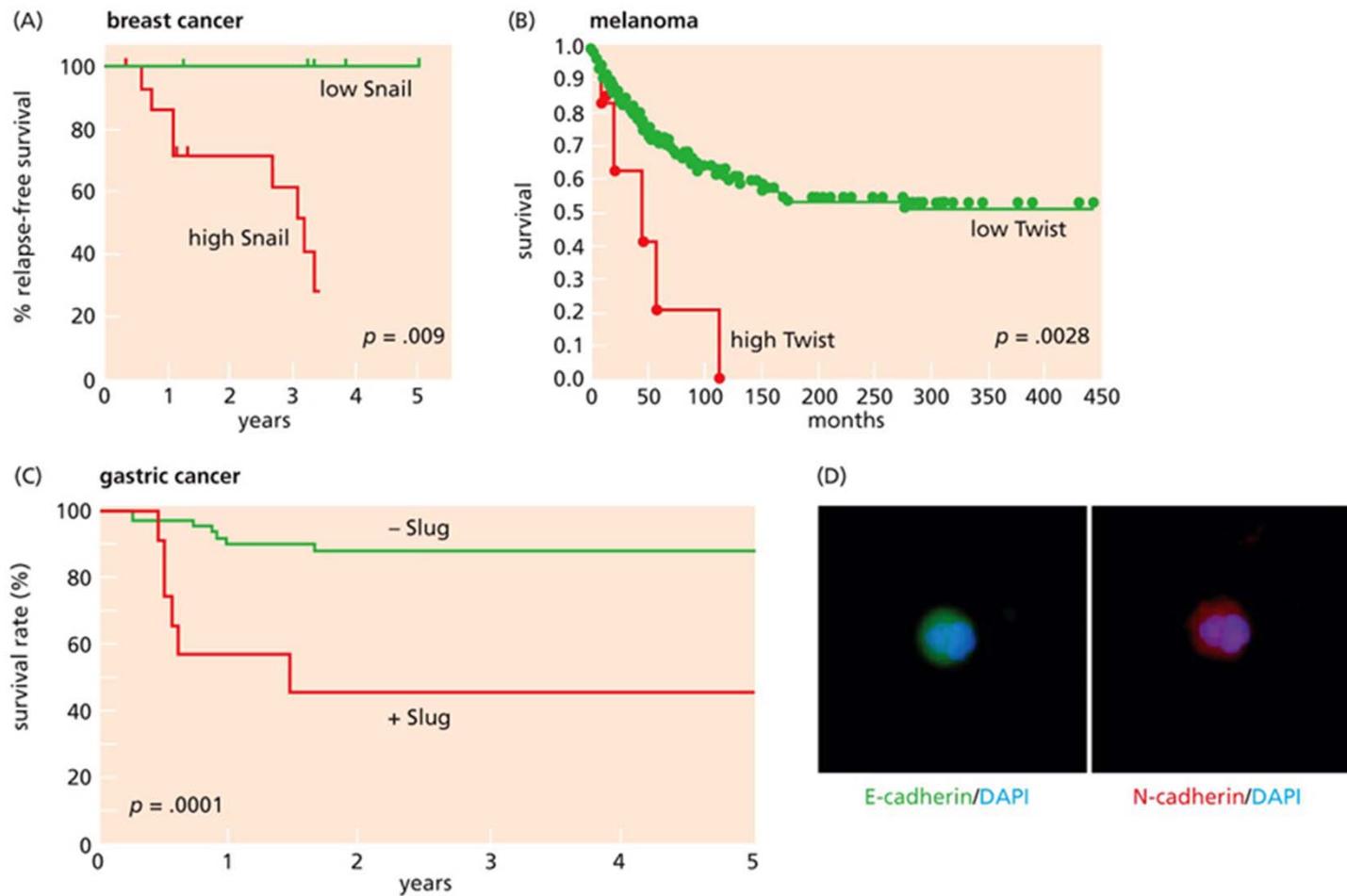


Figure 14.31 The Biology of Cancer (© Garland Science 2014)

EMT is associating to increased migration of epithelial cells

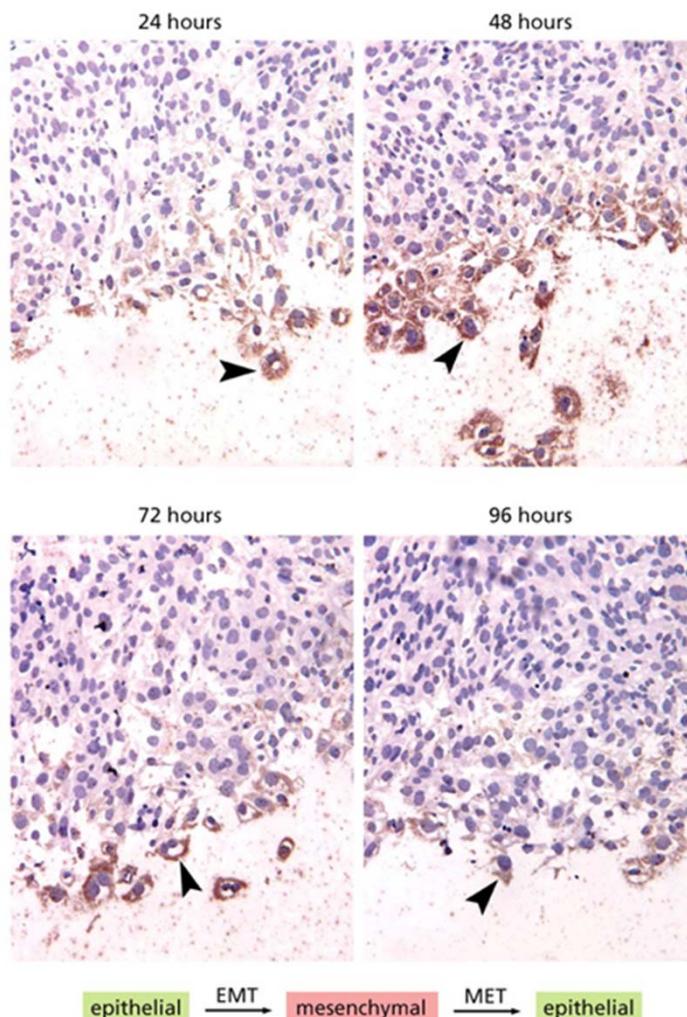


Figure 14.26 The Biology of Cancer (© Garland Science 2014)

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

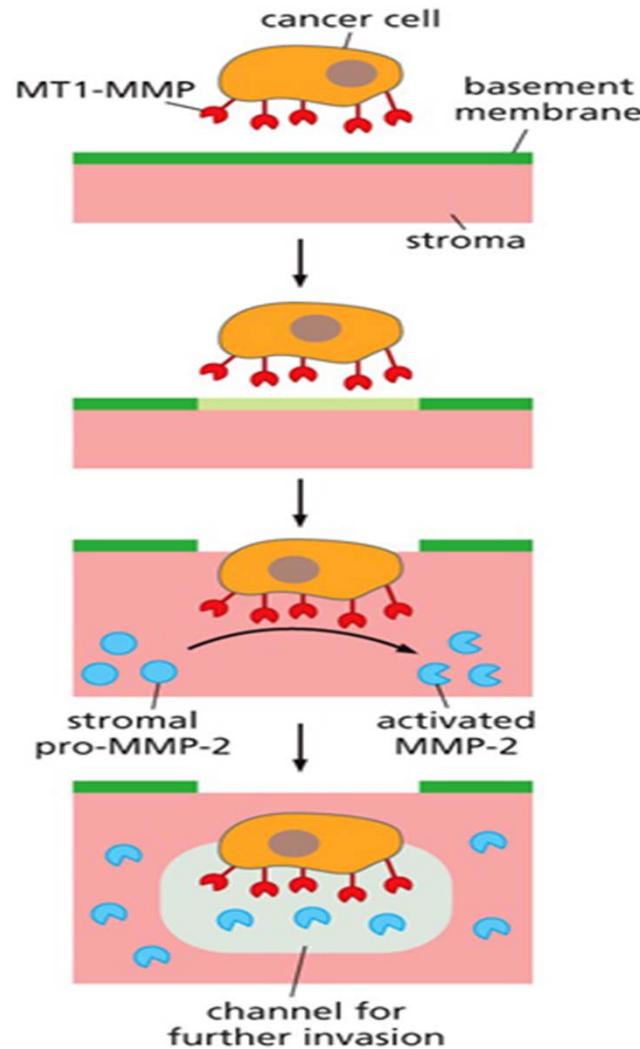


Figure 14.34 The Biology of Cancer (© Garland Science 2014)

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

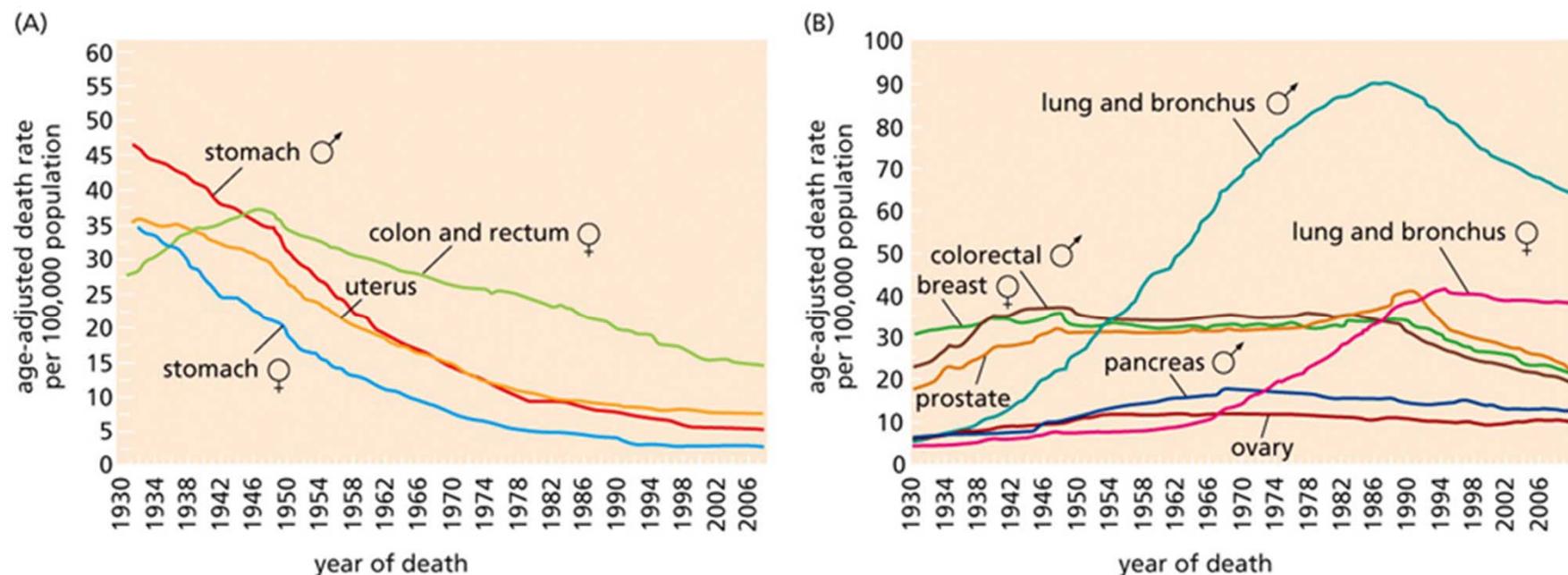


Figure 16.1 The Biology of Cancer (© Garland Science 2014)

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

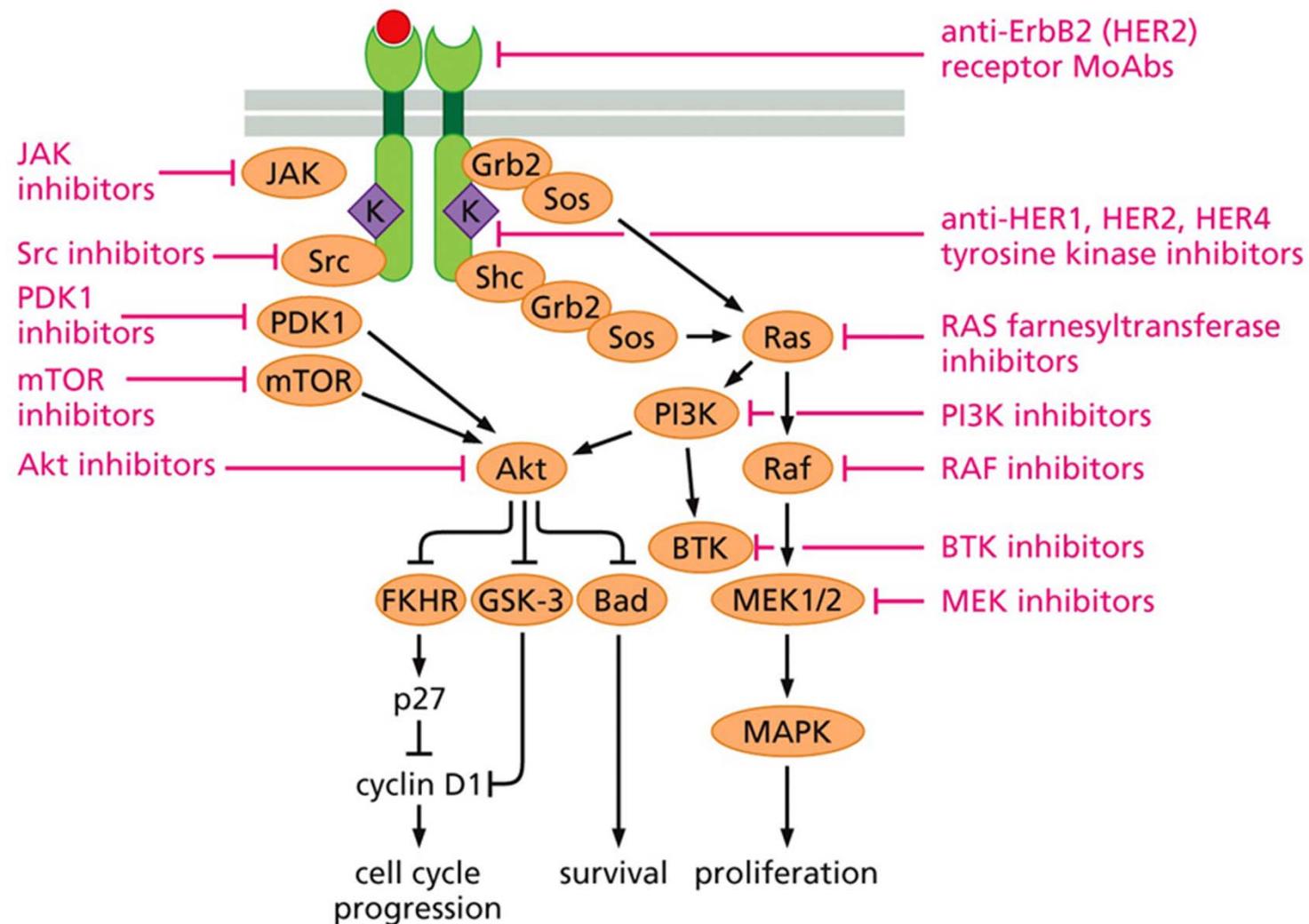


Figure 16.9 The Biology of Cancer (© Garland Science 2014)

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.

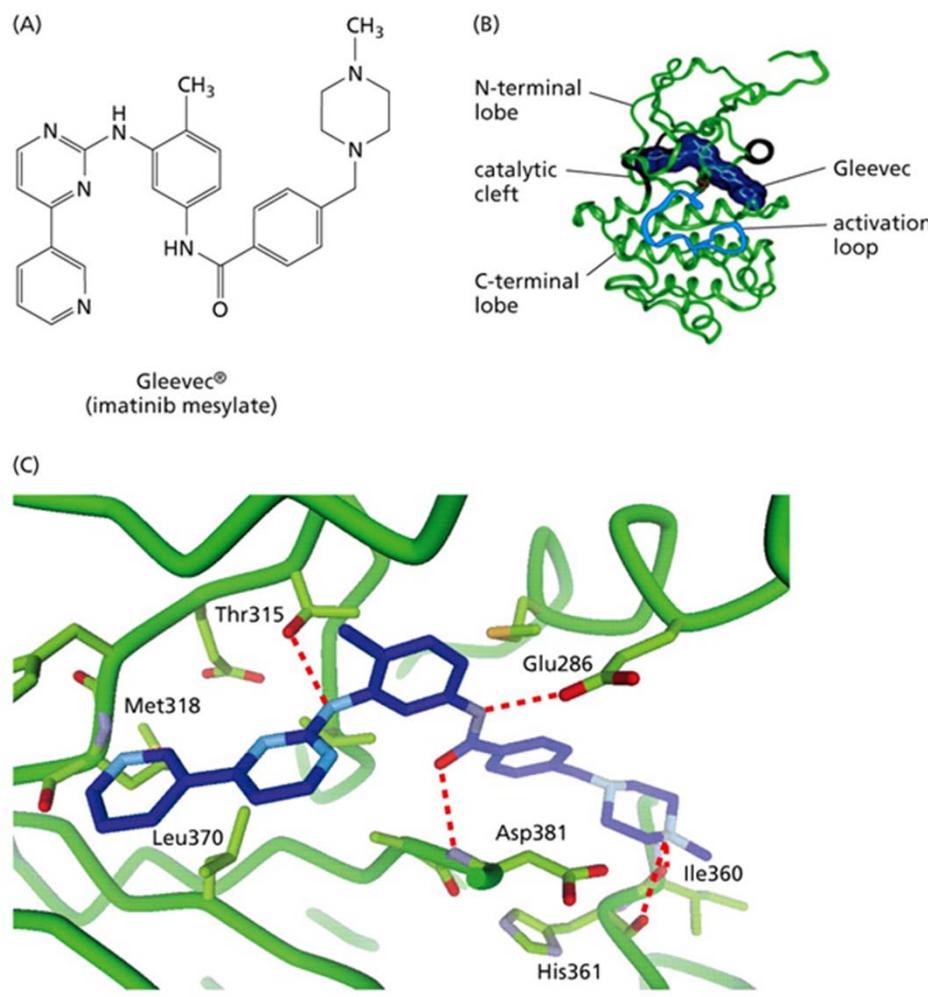


Figure 16.10 The Biology of Cancer (© Garland Science 2014)

Gleevec more specifically targets BCR-Abl versus other kinases

All kinase folds are similar

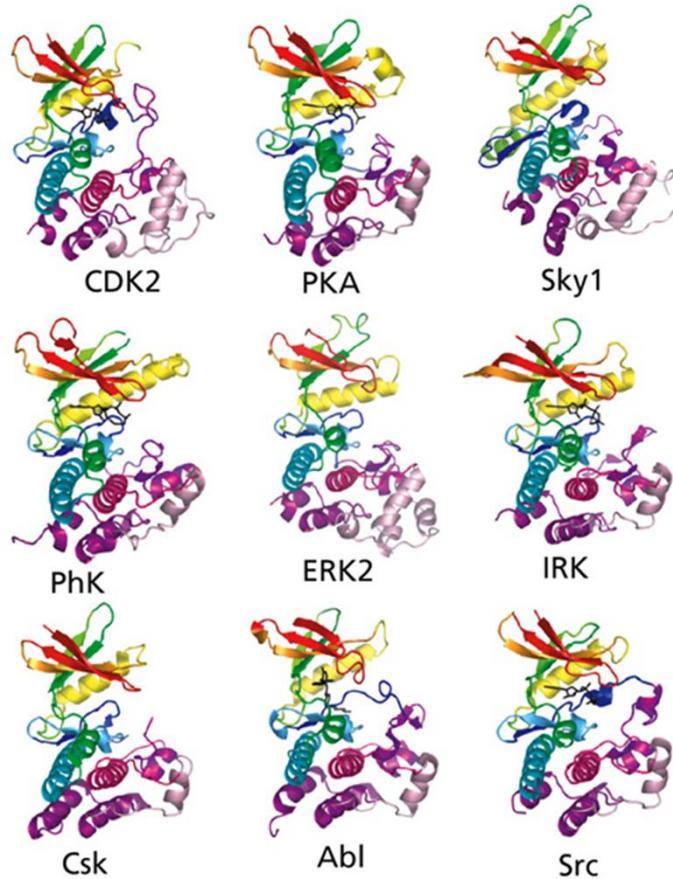


Figure 16.12a The Biology of Cancer (© Garland Science 2014)

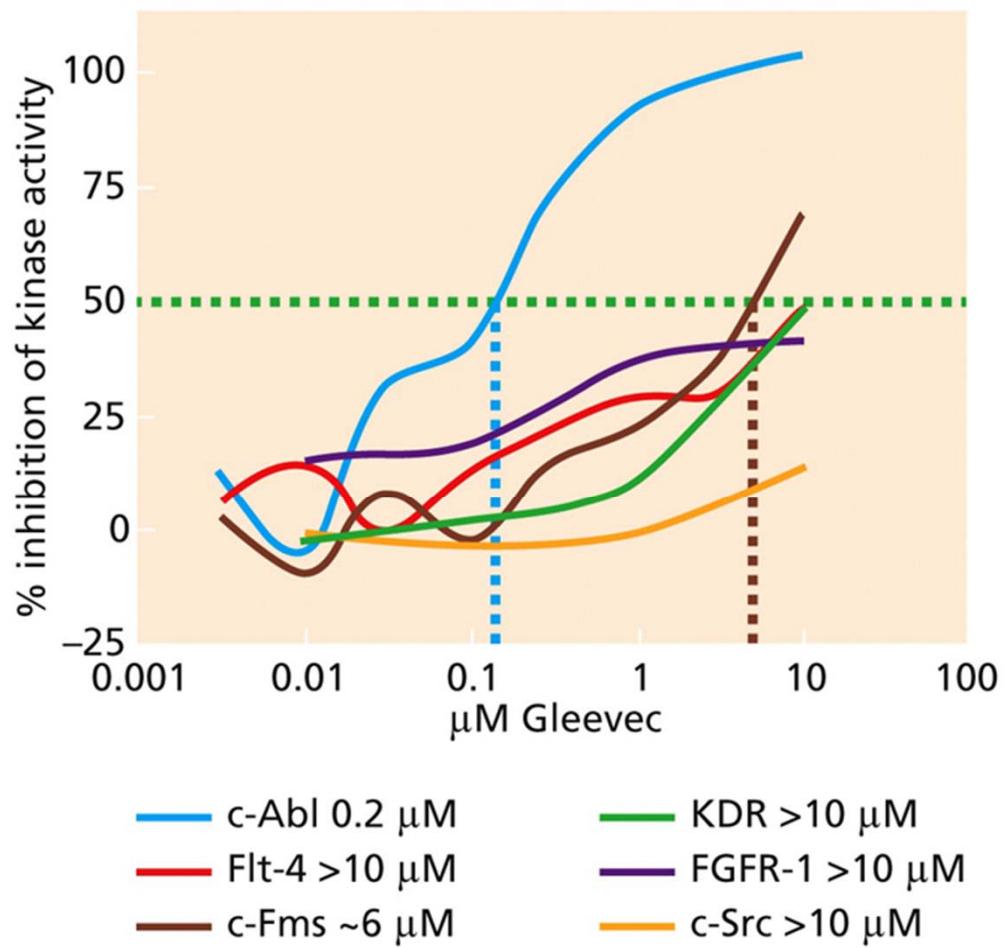


Figure 16.14 The Biology of Cancer (© Garland Science 2014)

Over the time, cancer develops 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 temozolomide 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 *crlk* 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 oncprotein. 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.

Table 16.5 The Biology of Cancer (© Garland Science 2014)

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



2018/12/15

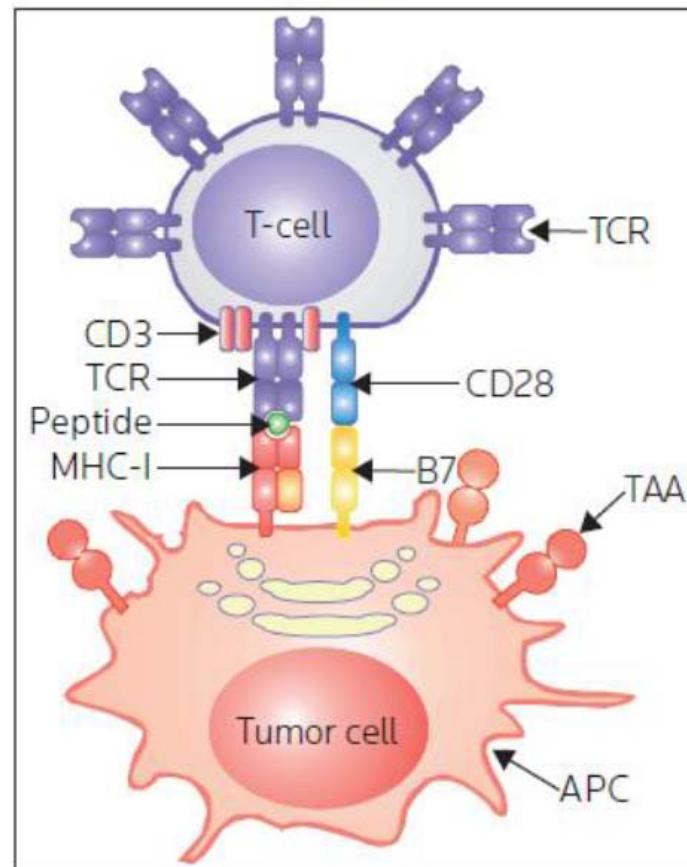
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Breakthrough of the Year 2013



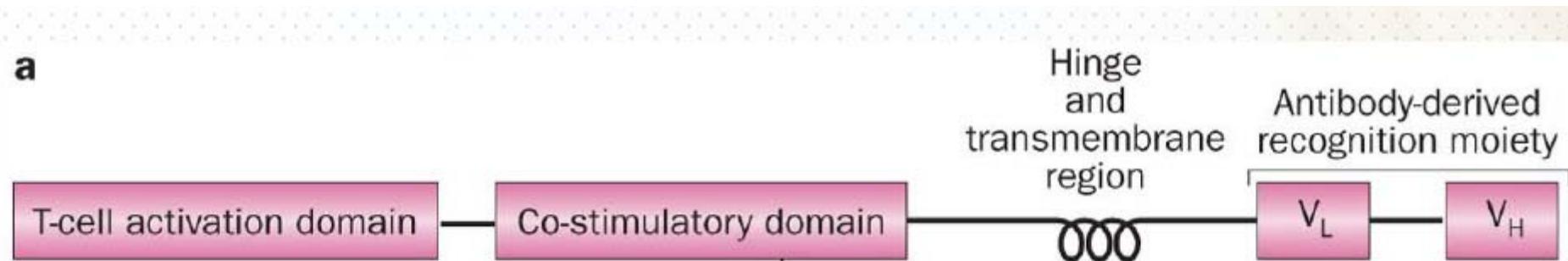
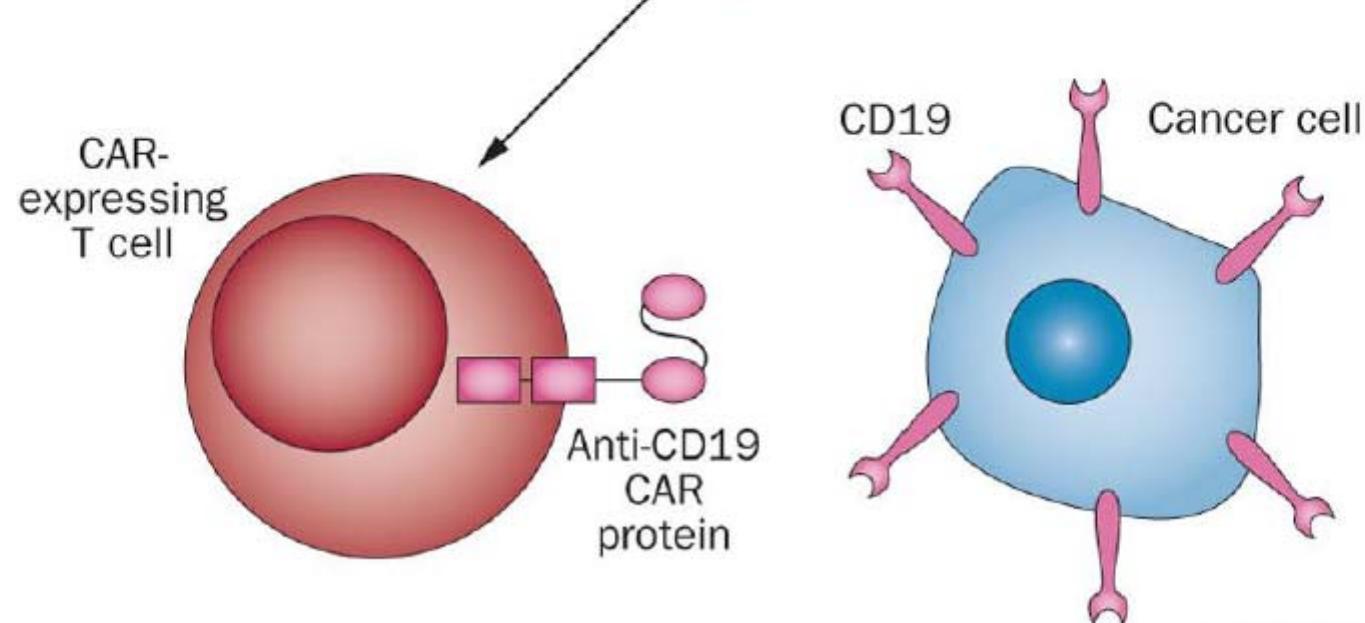
CANCER
IMMUNOTHERAPY

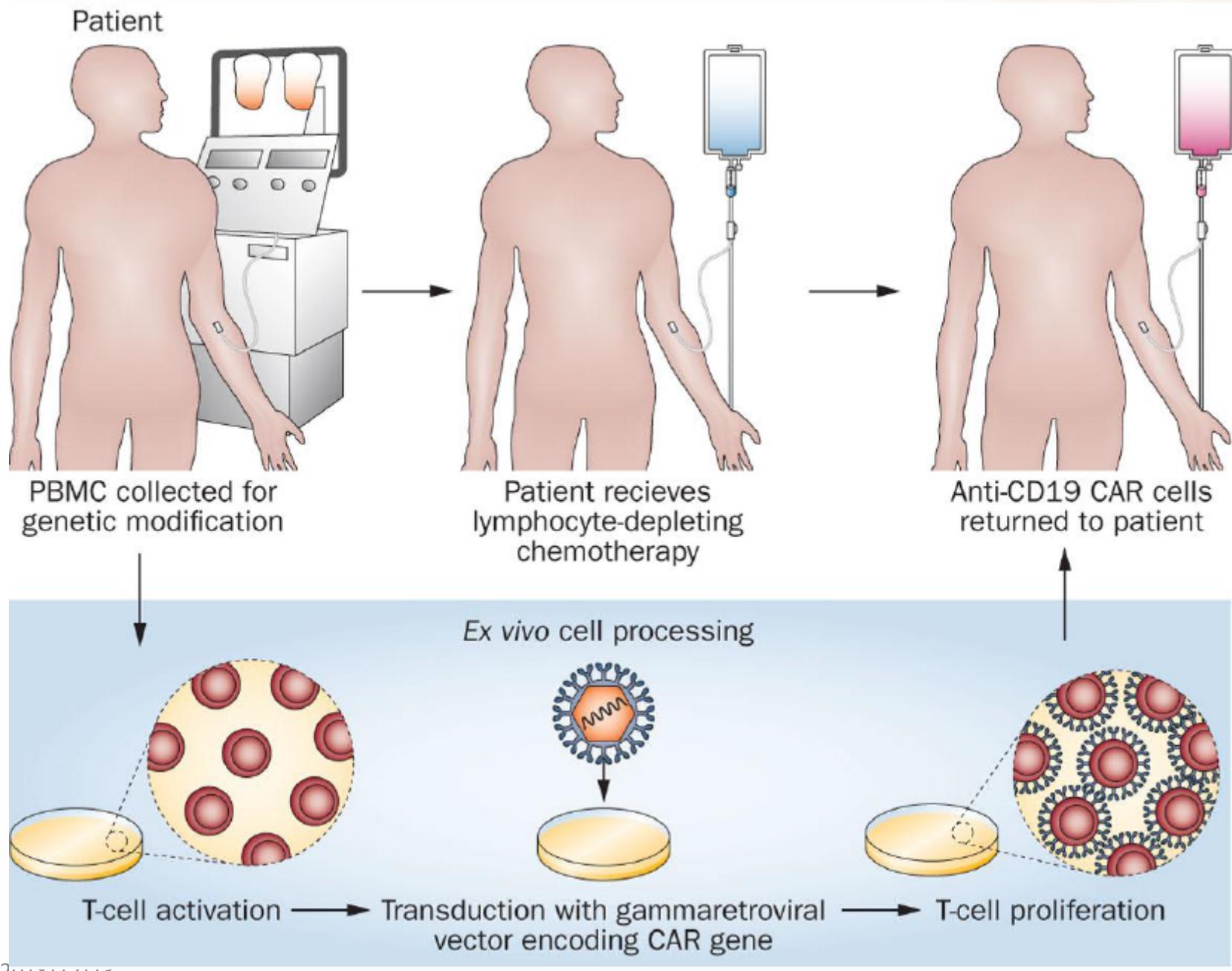
Regular

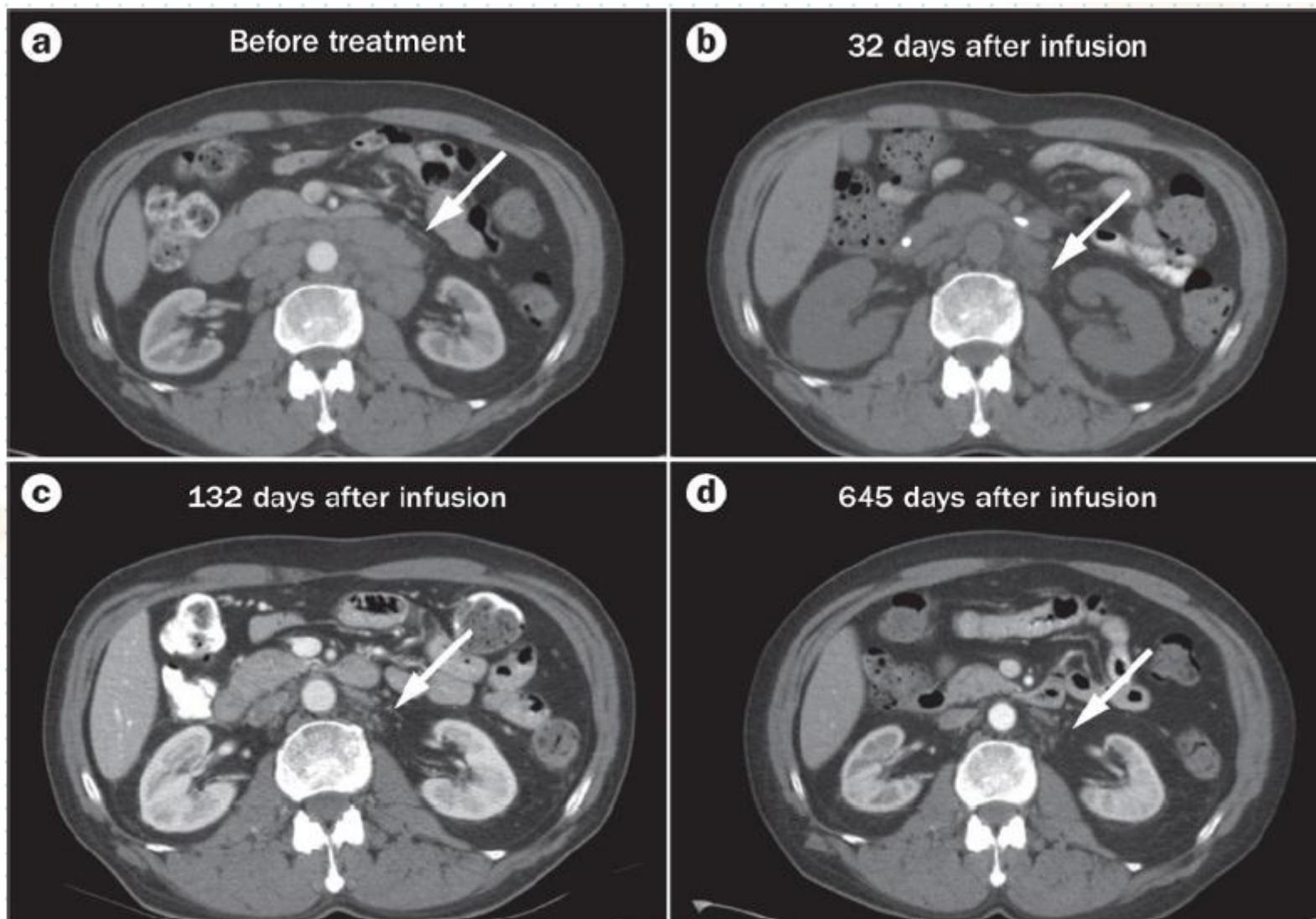


Elements required for specific T-cell response

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

a**b**





2018/12/13

Anti-PD-1 as a immunotherapy for tumors

