



# **Introduction: The basic biology of cancer**

## Origins of cancer?

Human cancers in Egyptian mummies 5,000 years old.

Cancer arose with advent of multi-cellularity 700 million years ago. Each cell gains the right to multiply independently. Must be mechanisms to tailor proliferation to the needs of the organism. Circumvention of those controls will lead to uncontrolled growth.

Human body contains  $3 \times 10^{13}$  cells. (30,000 billion).

Miracle is that regulatory systems have a less than 1 in  $3 \times 10^{13}$  chance of failing over the course of a human life time.

**Table 2.5 Geographic variation in cancer incidence and death rates**

Countries showing highest and lowest incidence of specific types of cancer <sup>a</sup>			
Cancer site	Country of highest risk	Country of lowest risk	Relative risk H/L <sup>b</sup>
Skin (melanoma)	Australia (Queensland)	Japan	155
Lip	Canada (Newfoundland)	Japan	151
Nasopharynx	Hong Kong	United Kingdom	100
Prostate	U.S. (African American)	China	70
Liver	China (Shanghai)	Canada (Nova Scotia)	49
Penis	Brazil	Israel (Ashkenazic)	42
Cervix (uterus)	Brazil	Israel (non-Jews)	28
Stomach	Japan	Kuwait	22
Lung	U.S. (Louisiana, African American)	India (Madras)	19
Pancreas	U.S. (Los Angeles, Korean American)	India	11
Ovary	New Zealand (Polynesian)	Kuwait	8

Geographic areas showing highest and lowest death rates from specific types of cancer <sup>c</sup>			
Cancer site	Area of highest risk	Area of lowest risk	Relative risk H/L <sup>b</sup>
Lung, male	Eastern Europe	West Africa	33
Esophagus	Southern Africa	West Africa	16
Colon, male	Australia, New Zealand	Middle Africa	15
Breast, female	Northern Europe	China	6

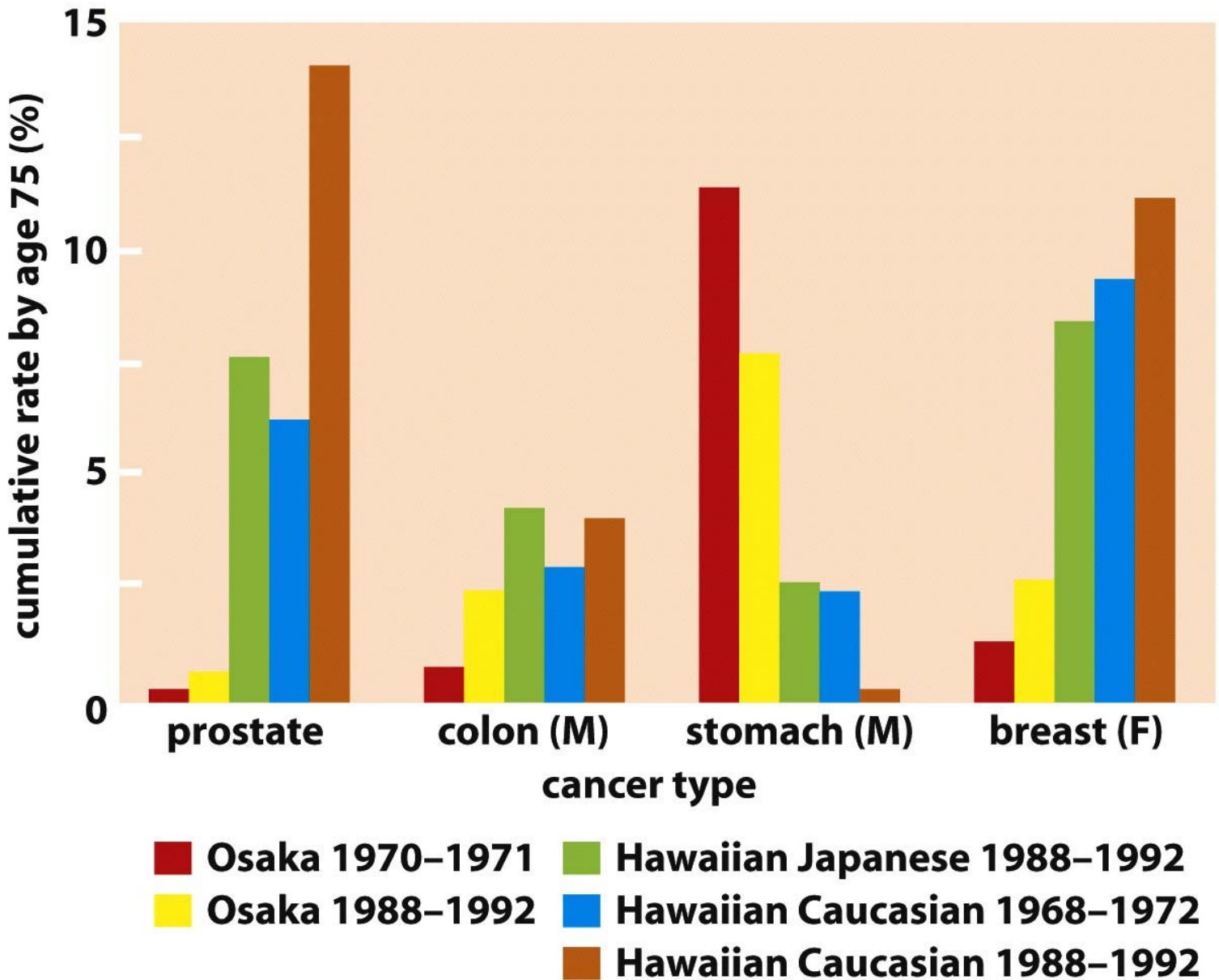


Figure 2-20 The Biology of Cancer (© Garland Science 2007)

## **Dietary factors and cancer:**

Stomach cancer 7x more common in Japan than USA.  
Colon cancer 1/20th incidence in Africa as USA

Unlikely to be genetic since Japanese migrating to Hawaii quickly adopt US pattern of cancer incidence.

90% of cancers are thought to be caused by environmental factors (not pollution/contaminants).

About 1-3% due to *occupational exposure*.

Most cancers seem to be caused by what we do to ourselves.

High fat/red meat diet, smoking. Lung cancer rare disease at turn of century.

## What causes cancer?

In 1775 sir Perceval Pott -high incidence scrotal cancer in chimney sweeps in Britain. Dutch chimney sweeps much lower (reason?).

Conclusion - something in soot induced cancer when in contact with skin for prolonged periods. Indication cancer has a cause that is external.

Today many examples of occupational exposure causing cancer:

Bladder cancer in rubber workers.

Mine workers exposed to uranium, asbestos, and radon - lung cancer.

Blast furnace crane operators – lung cancer.

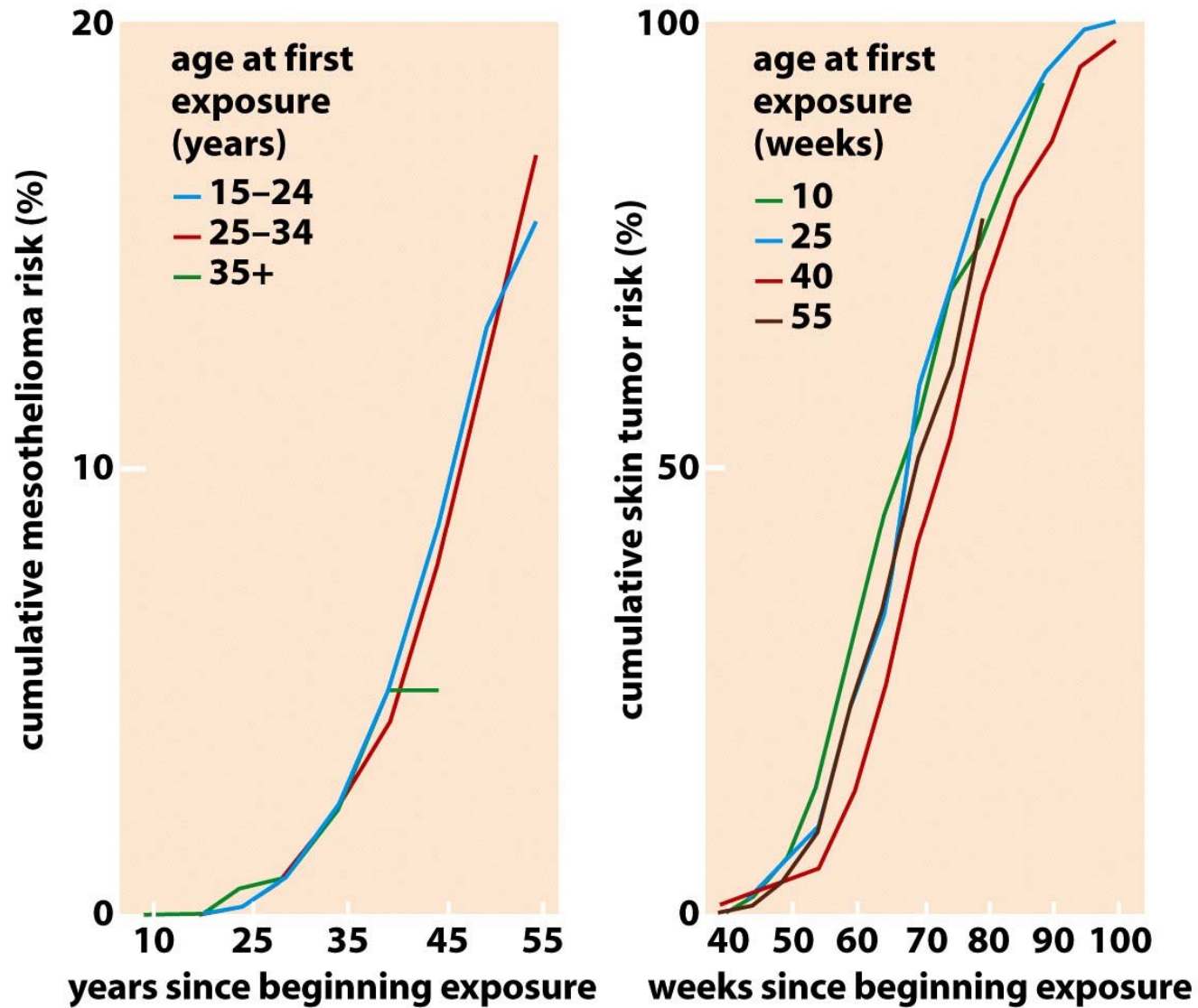


Figure 11-4 The Biology of Cancer (© Garland Science 2007)

**Table 2.6** Relative risk of lung cancer as a function of the number of cigarettes smoked per day<sup>a</sup>

	Lifelong nonsmoker	Smokers			
Most recent number of cigarettes smoked (by subjects) per day before onset of disease	—	≥1, <5	≥5, <15	≥15, <25	≥25
Relative risk	1	8	12	14	27

<sup>a</sup>The relative risk indicates the risk of contracting lung cancer compared with that of a nonsmoker, which is set at 1. (From R. Doll and A.B. Hill, *BMJ* 2:739–748, 1950.)

Table 2-6 The Biology of Cancer (© Garland Science 2007)



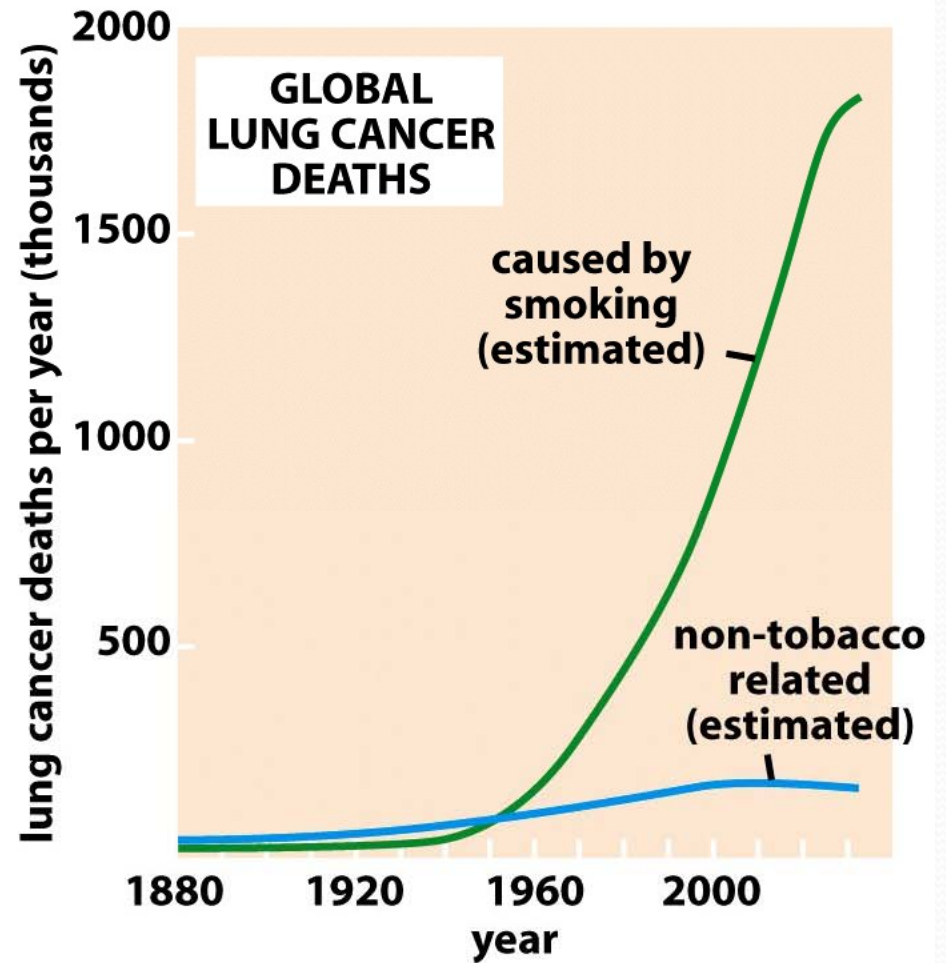
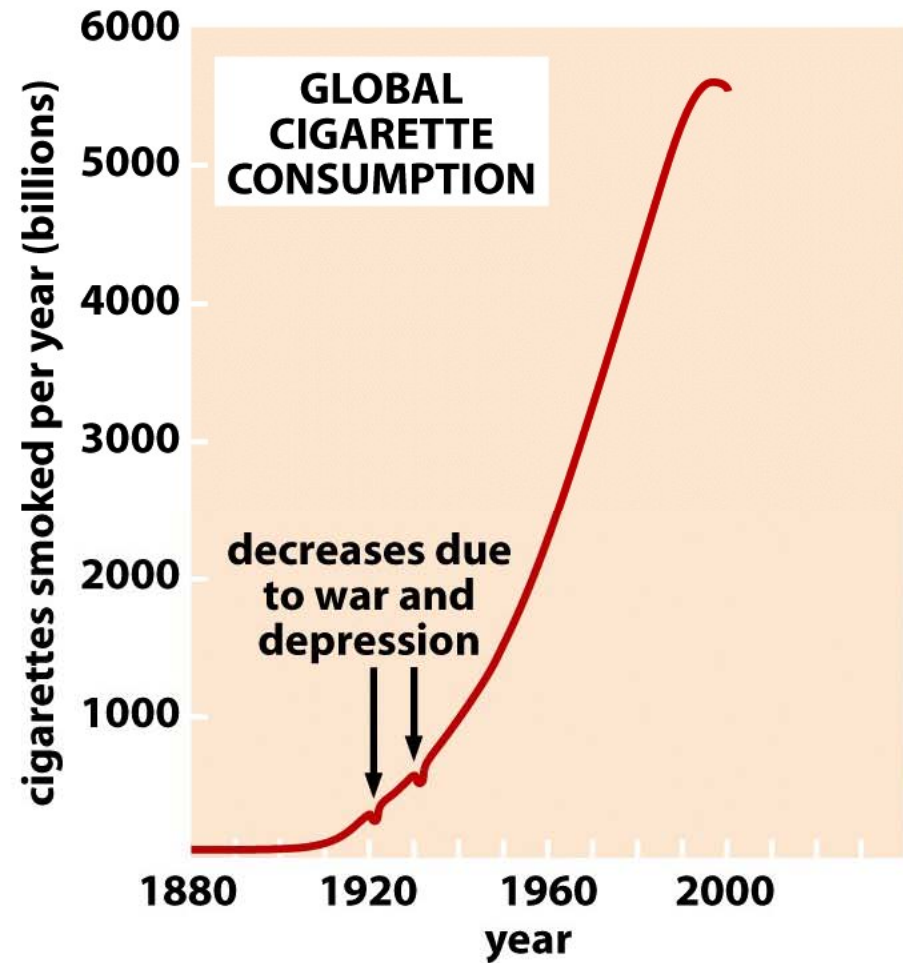


Figure 11-2 The Biology of Cancer (© Garland Science 2007)

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**Table 2.7 Known or suspected causes of human cancers**

<b>Environmental and lifestyle factors known or suspected to be etiologic for human cancers in the United States<sup>a</sup></b>	
<b>Type</b>	<b>% of total cases<sup>b</sup></b>
<b>Cancers due to occupational exposures</b>	<b>1–2</b>
<b>Lifestyle cancers</b>	
<b>Tobacco-related (sites: e.g., lung, bladder, kidney)</b>	<b>34</b>
<b>Diet (low in vegetables, high in nitrates, salt) (sites: e.g., stomach, esophagus)</b>	<b>5</b>
<b>Diet (high fat, lower fiber, broiled/fried foods) (sites: e.g., bowel, pancreas, prostate, breast)</b>	<b>37</b>
<b>Tobacco and alcohol (sites: mouth, throat)</b>	<b>2</b>

<b>Specific carcinogenic agents implicated in the causation of certain cancers<sup>c</sup></b>	
<b>Cancer</b>	<b>Exposure</b>
<b>Scrotal carcinomas</b>	<b>chimney smoke condensates</b>
<b>Liver angiosarcoma</b>	<b>vinyl chloride</b>
<b>Acute leukemias</b>	<b>benzene</b>
<b>Nasal adenocarcinoma</b>	<b>hardwood dust</b>
<b>Osteosarcoma</b>	<b>radium</b>
<b>Skin carcinoma</b>	<b>arsenic</b>
<b>Mesothelioma</b>	<b>asbestos</b>
<b>Vaginal carcinoma</b>	<b>diethylstilbestrol</b>
<b>Oral carcinoma</b>	<b>snuff</b>

**Table 2.8** A sampling of Bruce Ames's roster of carcinogens identified in the normal diet<sup>a</sup>

<b>Foodstuff</b>	<b>Compound</b>	<b>Concentration in foodstuff</b>
Black pepper	piperine	100 mg/g
Common mushroom	agaritine	3 mg/g
Celery <sup>b</sup>	furocoumarins, psoralens	1 µg/g, 0.8 µg/g
Rhubarb	anthraquinones	varies
Cocoa powder	theobromine	20 mg/g
Mustard, horseradish	allyl isothiocyanate	varies
Alfalfa sprouts	canavanine <sup>c</sup>	15 mg/g
Burnt materials <sup>d</sup>	large number	varies
Coffee	caffeic acid	11.6 mg/g

## **Spoiled food - carcinogenic:**

Introduction food preservatives and refrigeration - 6-7 x decrease in stomach cancer in US (anti-food preservative lobbyists) –moulds produce carcinogenic compounds.

## **Smoking can be hazardous to your health:**

Lung cancer very rare at turn of 20<sup>th</sup> century.

Today in USA 450,000 to 500,000 die each year from smoking related disease (55,000 US servicemen died in the Vietnam war).

Smoking increase incidence of lung cancer but also bladder cancer, lymphoma, esophageal cancer, prostate cancer, breast cancer, mouth cancer). In women incidence of lung cancer will soon pass colorectal cancer (Virginia Slims).

## **Western diet:**

Red meat diet high in saturated fats increased incidence colon cancer (mechanism unknown). Adopting vegetarian diet estimated to reduce incidence colorectal cancer by 70-80%. *Not smoking and dietary change could reduce incidence of cancer overall by 50-60%.*

# Cancer is a multistep process: 6-7 events required

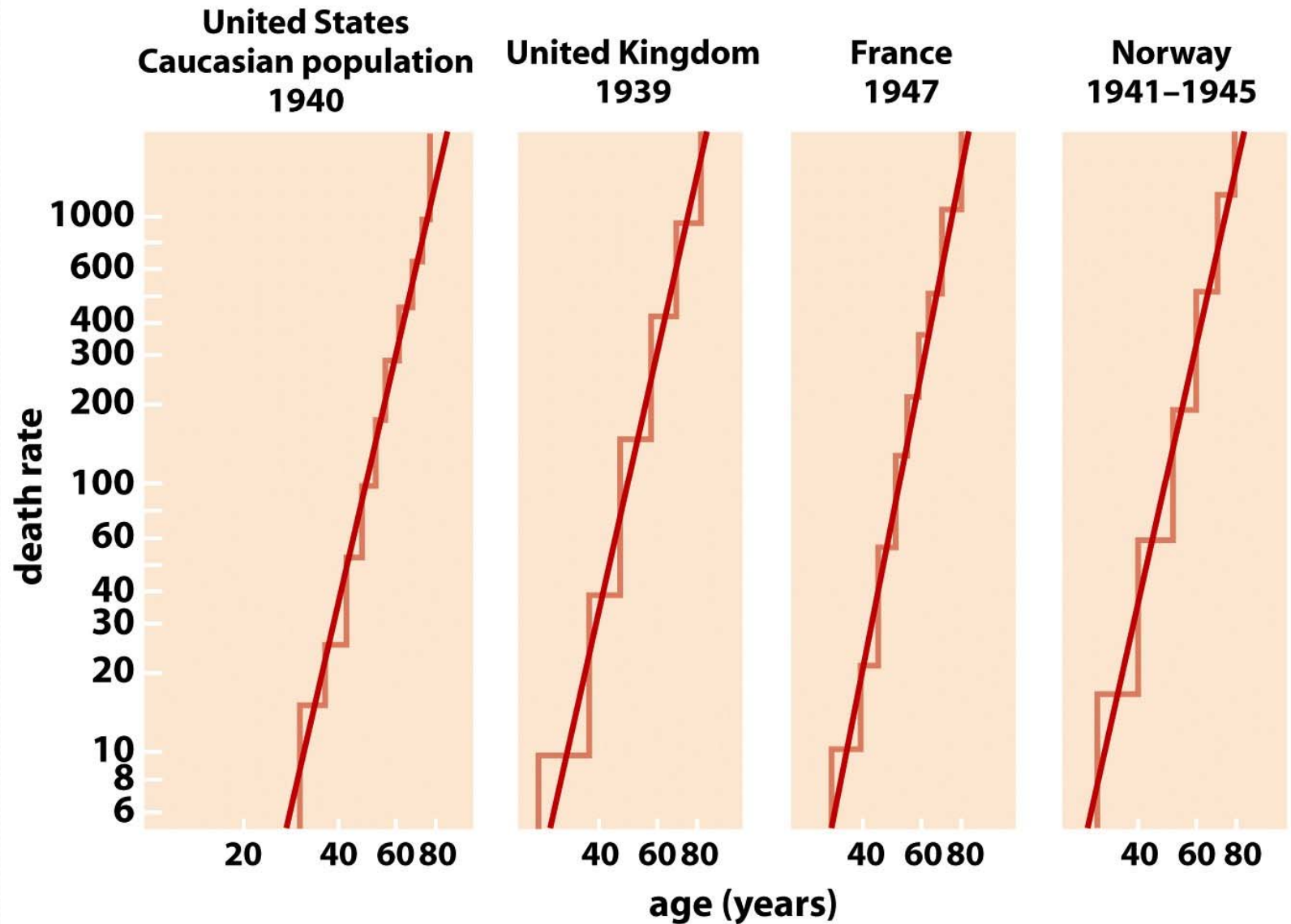
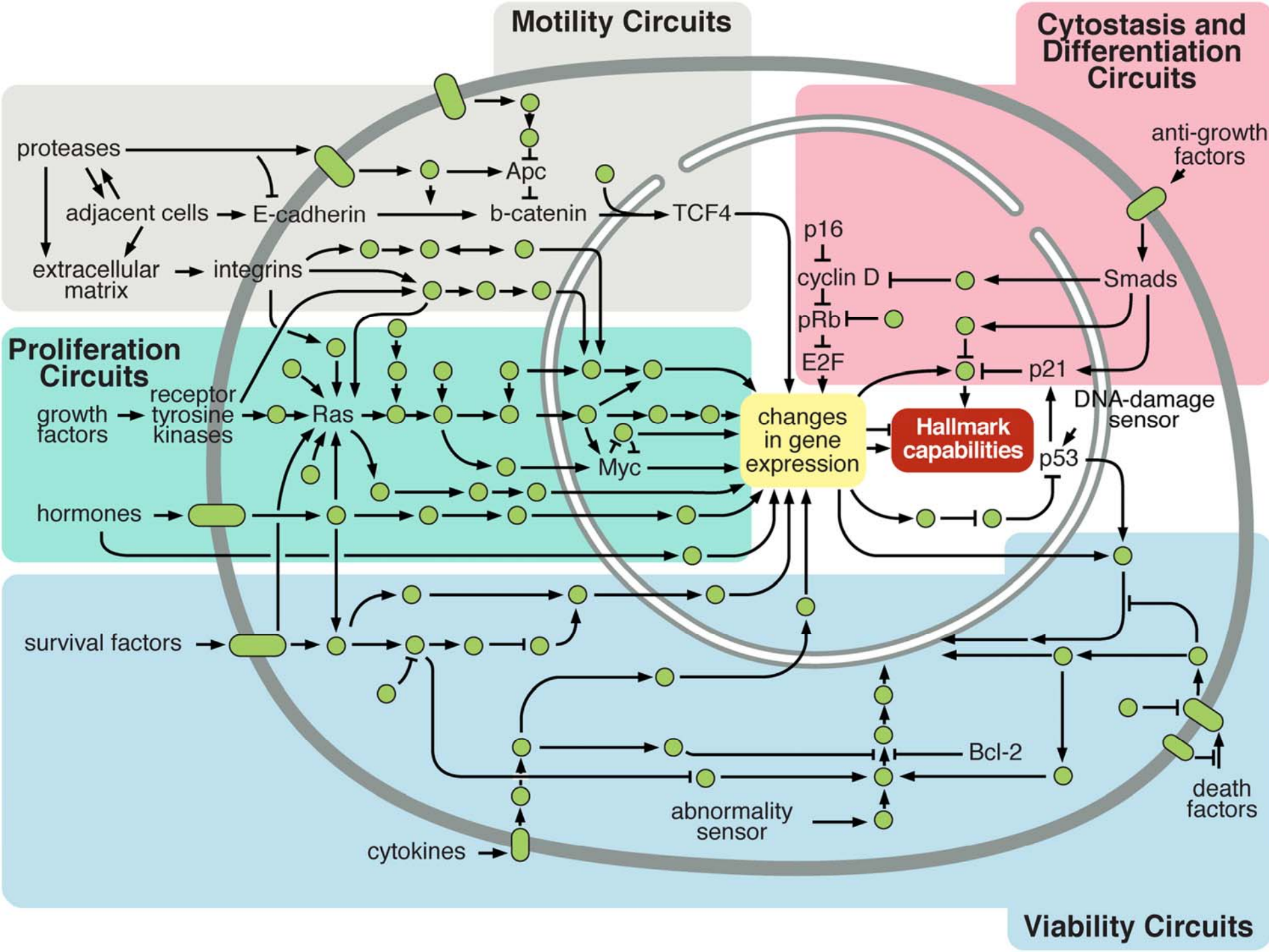


Figure 11-3 The Biology of Cancer (© Garland Science 2007)



## Loss of tumor suppressors during development of colorectal cancer

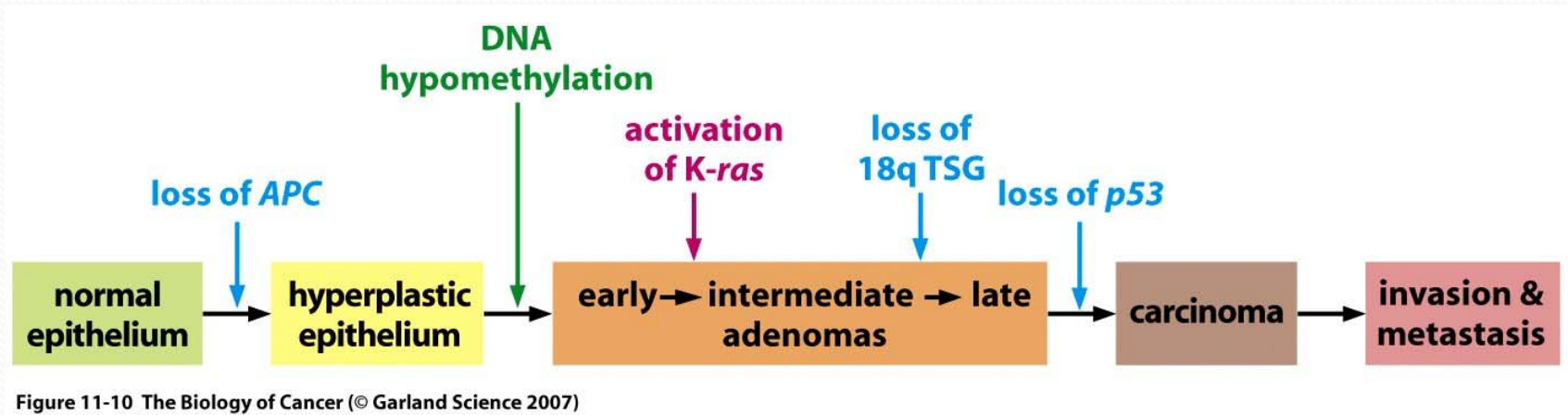


Figure 11-10 The Biology of Cancer (© Garland Science 2007)



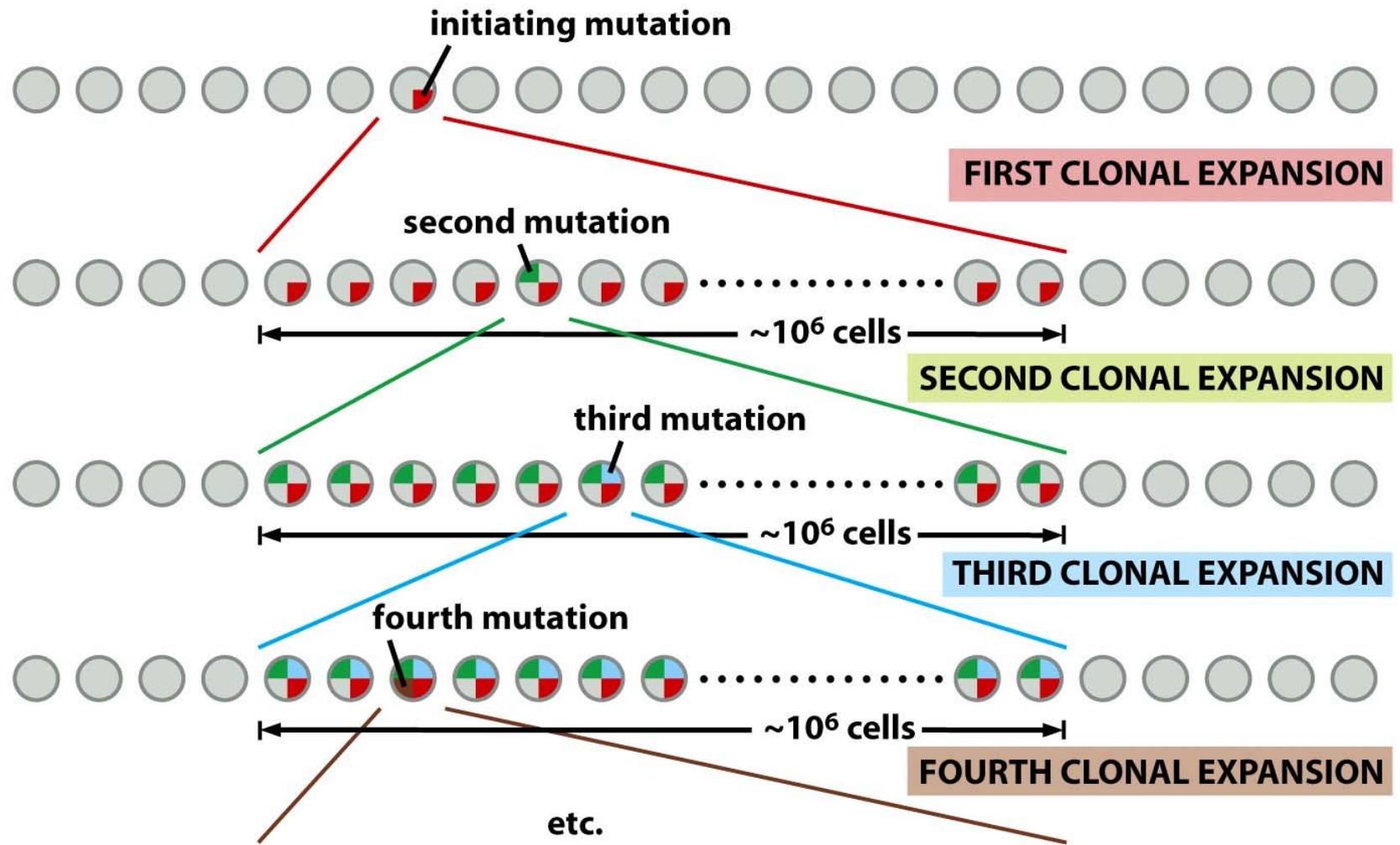


Figure 11-12 The Biology of Cancer (© Garland Science 2007)

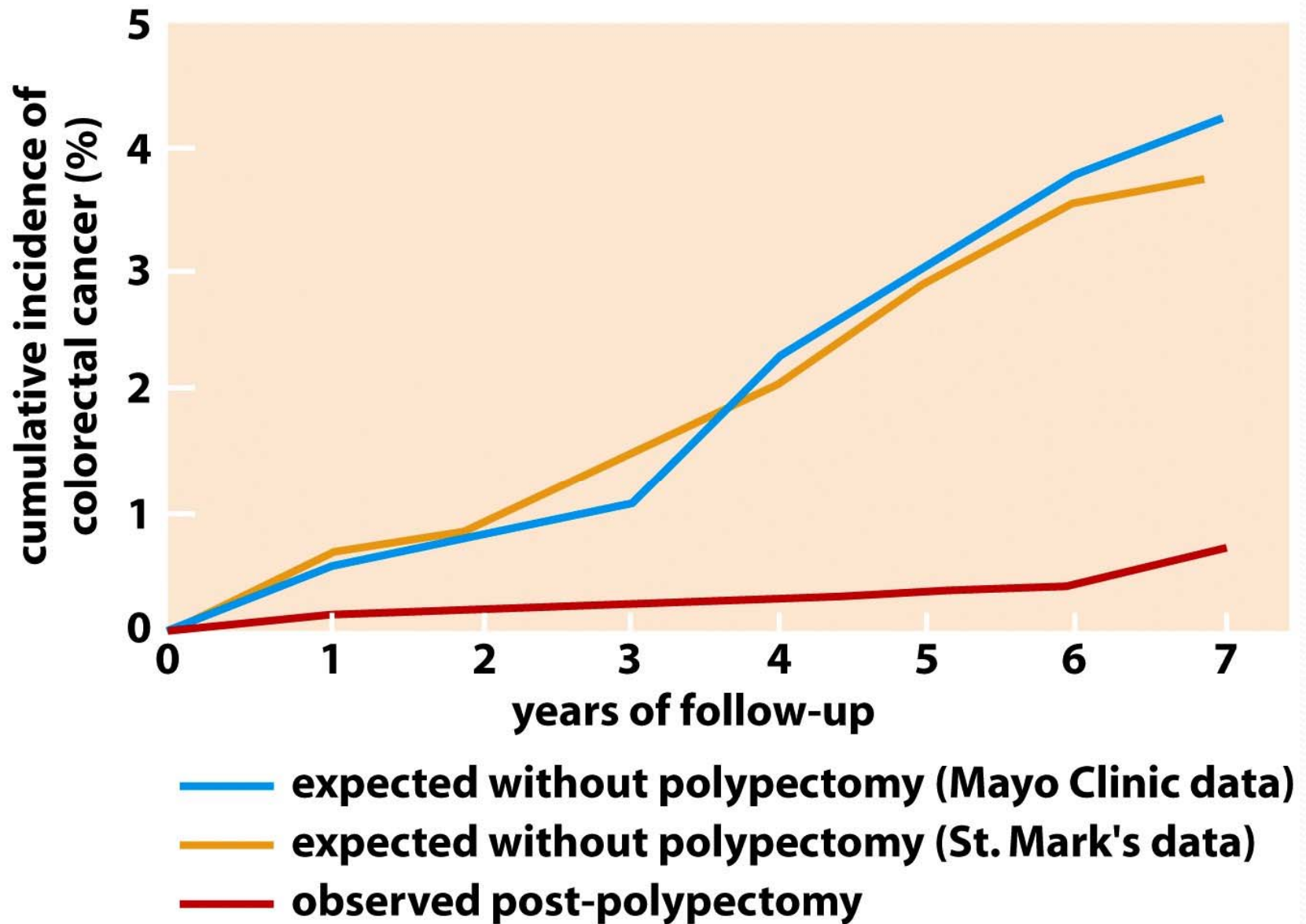


Figure 11-8b The Biology of Cancer (© Garland Science 2007)

## **Is there a cancer epidemic?**

### **Improved detection:**

Following the diagnosis of Betty Ford's breast cancer the incidence of breast cancer in the US rose by 30%.

The incidence of prostate cancer detection increased dramatically following introduction of the PSA test.

Will enhanced detection result in decreased mortality? For most cancers probably not.

Lung cancer screening - no benefit.

Breast cancer mortality decreasing but due to improved treatment.

Prostate cancer mortality-questionable.

Colorectal cancer screening by colonoscopy has decreased mortality because macroscopic pre-malignant lesions can be detected and excised (special case).



Tumors arise through loss of proliferative regulatory signals.

Yeast genome - 9,000 genes

Fly genome 20,000

Worm genome 19,000

Human genome 30,000 genes (100,000 predicted based on complexity).

Of these 500-1000 regulate cell proliferation and growth.

Humans have inherited highly conserved regulatory systems evolved to protect multi-cellular organisms against renegade cell proliferation.

## 1. Sustained proliferative signaling.

Normal tissues control production and release of growth promoting signals that regulate entry into and progression through the growth cycle. Basis of tissue and organ homeostasis.

Cancer cells deregulate these signals and thereby master their own destiny. The enabling signals are conveyed in large part by growth factors that bind to and activate growth factor receptors (typically containing tyrosine kinase domains). These receptors emit intracellular signals that regulate progression through the cell cycle and increase in cell size.

A decade ago growth signaling in **normal tissues** was poorly understood. Part of the problem is that growth factor signals are transmitted in a temporal and spatially regulated pattern. This paracrine form of signaling is difficult to investigate experimentally because:

It requires the maintenance of tissue integrity.

Bioavailability of growth factors -regulated by solid-state fixation on the extracellular matrix and release through network of proteases in a highly localized manner.

By contrast mitogenic signaling in cancer cells (which are freed of tissue constraints) is easier to approach.

Cancer cells may:

Produce growth factor ligands that stimulate cognate receptors on the same cell.

Signal NORMAL CELLS within tumor stroma to supply growth factors.

Elevate LEVELS of receptors at the cell surface - increase responsiveness to ligand.

Induce structural changes in receptor allowing it to fire in absence of ligand.

Constitutively activate downstream receptor signaling pathways.

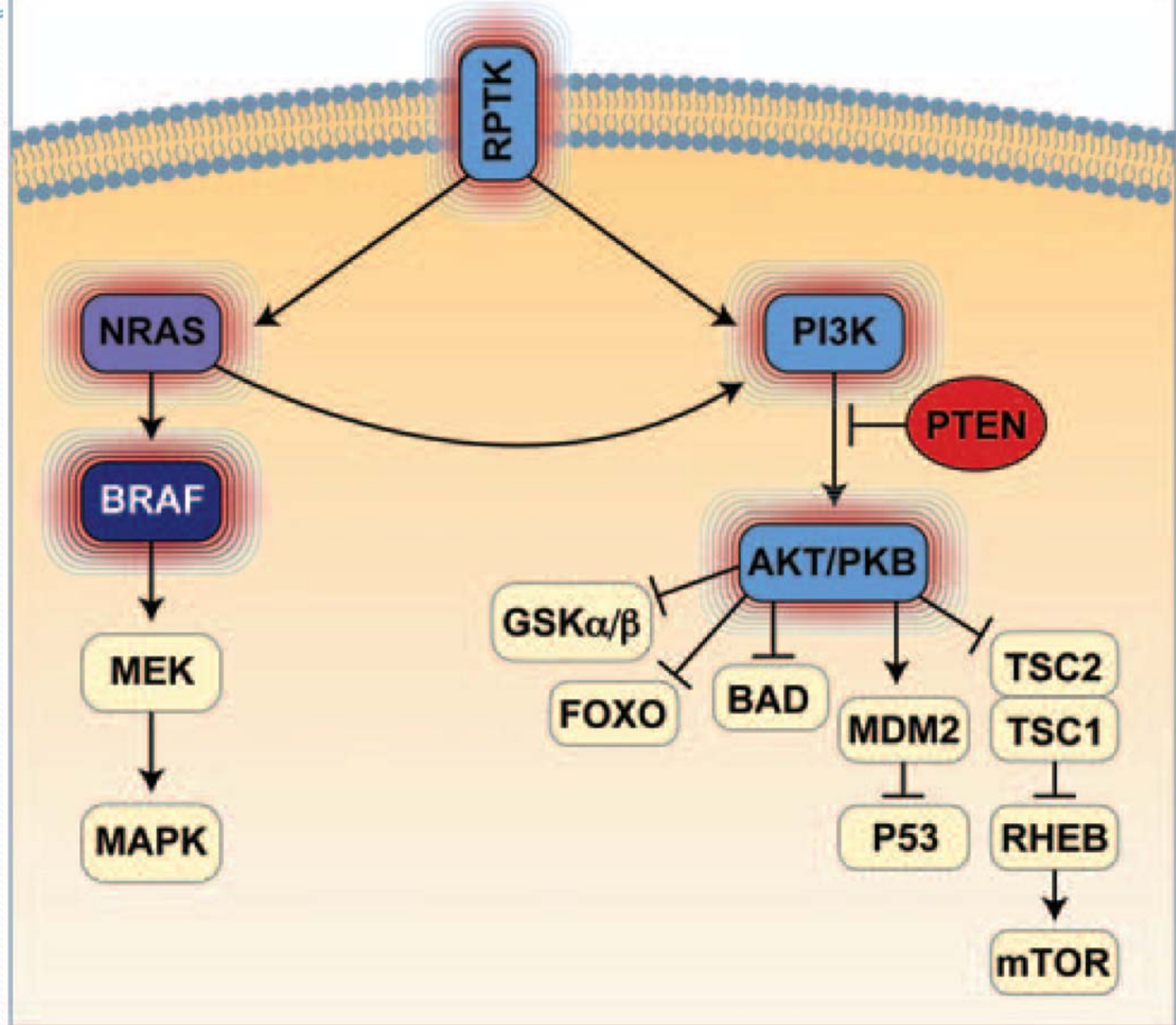
## 2. Somatic mutations activate additional downstream signals

DNA sequencing-somatic mutations in growth factor signaling.

40% human melanomas contain activating mutations in B-raf leading to constitutive activation of MAP kinase.

Mutations in PI3-kinase –hyperactivate PI3 K signaling-Akt/PKB signal transducer.

Point mutations in malignant melanoma:





## **Malignant melanoma:**

68,000 pts diagnosed annually in US 8,500 will die

From 1950-2000 6x increase in incidence

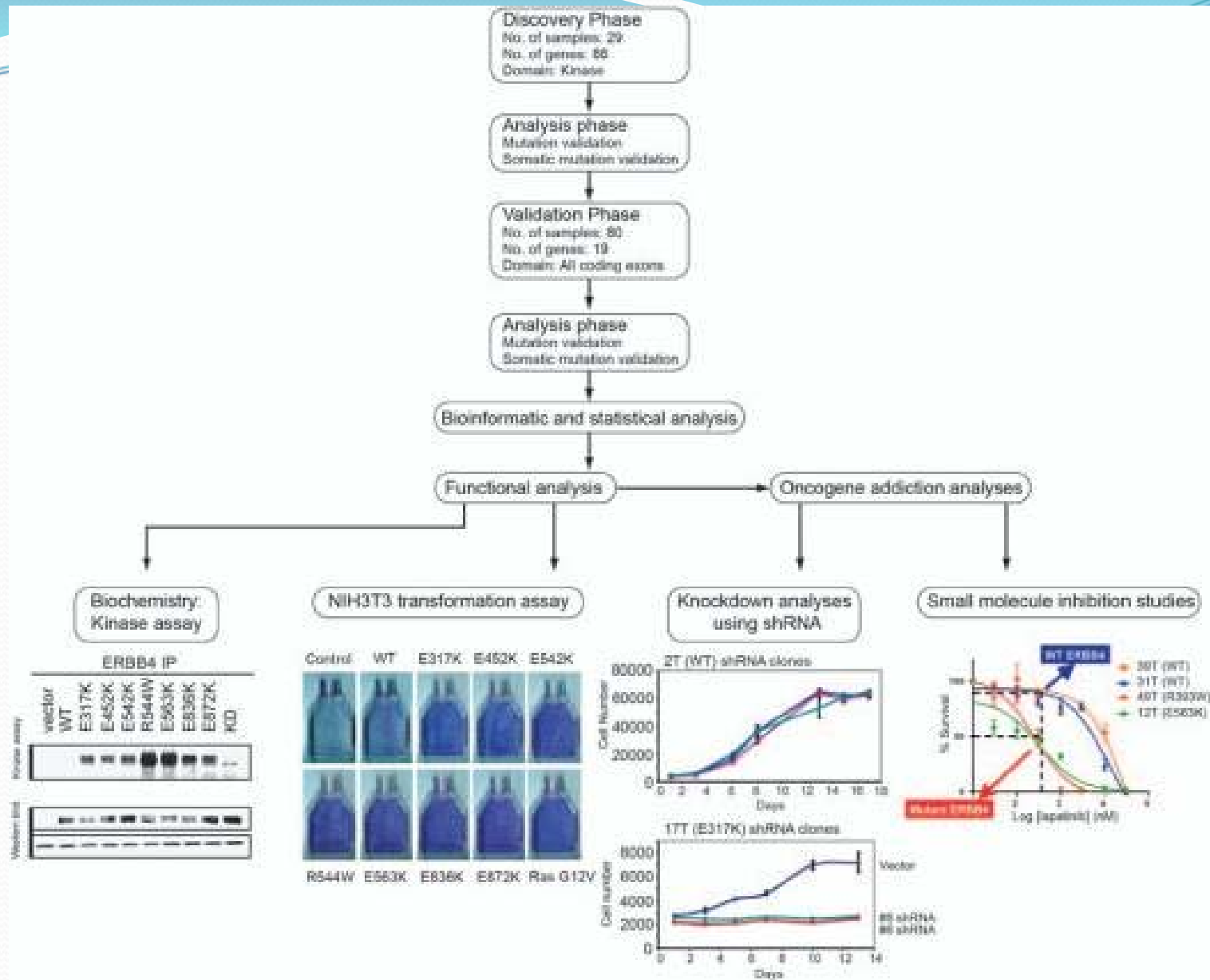
Only 6% of patients have sustained clinical responses to current treatment

BRAF mutations in 1-10% varietal tumors

BRAF mutations in over 50% melanoma patients

Sorafenib small molecule inhibitor of BRAF did not increase clinical response

HOWEVER, PLX4032, small molecule inhibitor selective against V600 mutant BRAF 70% clinical response



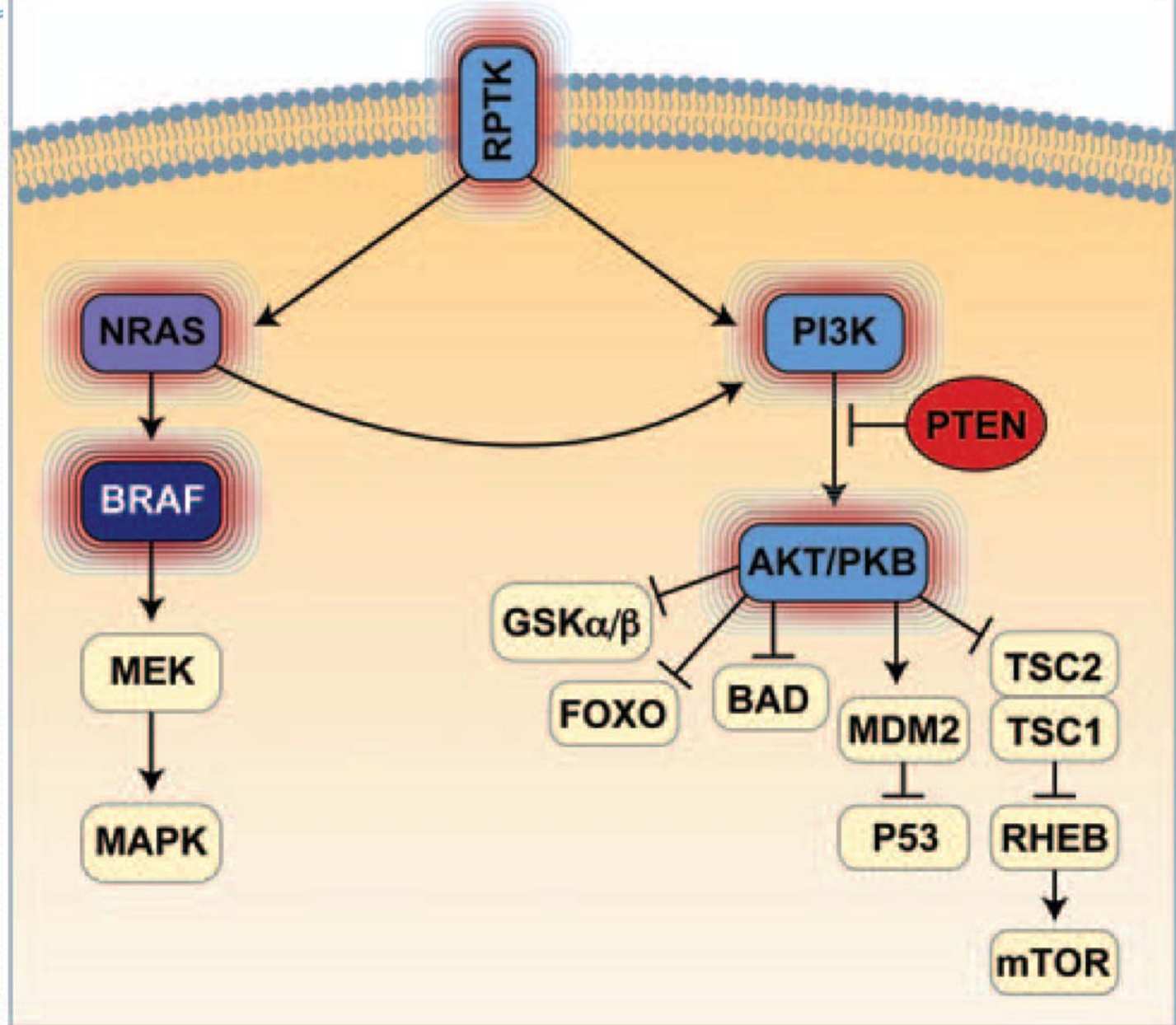
## **Targeted therapy in melanoma-tyrosine kinases:**

Systematic approach to identifying somatic mutations in tyrosine kinases identified ERBB<sub>4</sub> as the most highly mutated tyrosine kinase in melanoma

shRNA knockdown very effective in xenografts

Likely to be an effective new therapeutic agent

Point mutations in malignant melanoma:



### **3. Disruption of Negative-Feedback Mechanisms attenuate proliferative signaling**

Negative feedback loops: oncogenic effects of Ras do not arise from hyperactivation but from impairment of GTPase activity that normally ensures GTP signaling is transitory. Analogous mechanisms affect multiple nodes within proliferative signaling.

For example PTEN phosphatase counters PI3K by degrading PIP3. Loss of function in PTEN amplify PI3K signaling and promote tumorigenesis.

PTEN expression is commonly inhibited by methylation in human tumors.

mTOR kinase, coordinator of growth and metabolism up and down stream of PI3K. mTOR activation can lead to impaired PI3K signaling. Rapamycin inhibition of mTOR results in loss of negative feedback and activation of PI3K and AKT. Disruption of negative feedback loops only recently discovered and likely to be an important principle in oncogenesis.

## **4. Excessive proliferative signaling triggers senescence**

Excessive oncogenic signaling (RAS, MYC, RAF) trigger senescence and/or apoptosis.

Oncogenesis is therefore likely a balance between too little and too much proliferative signaling.

Some cancer cells may adapt to high levels of oncogenic signaling by disrupting senescence mechanisms.

## **5. Evading growth suppressors**

Cancer cells must also circumvent powerful tumor suppressor programs that negatively regulate proliferation. Many depend upon suppressor genes. Many suppressors have been validated by gain/loss function experiments in mice.

RB and TP53 are prototypic examples-pro-proliferation and pro-cell death respectively.

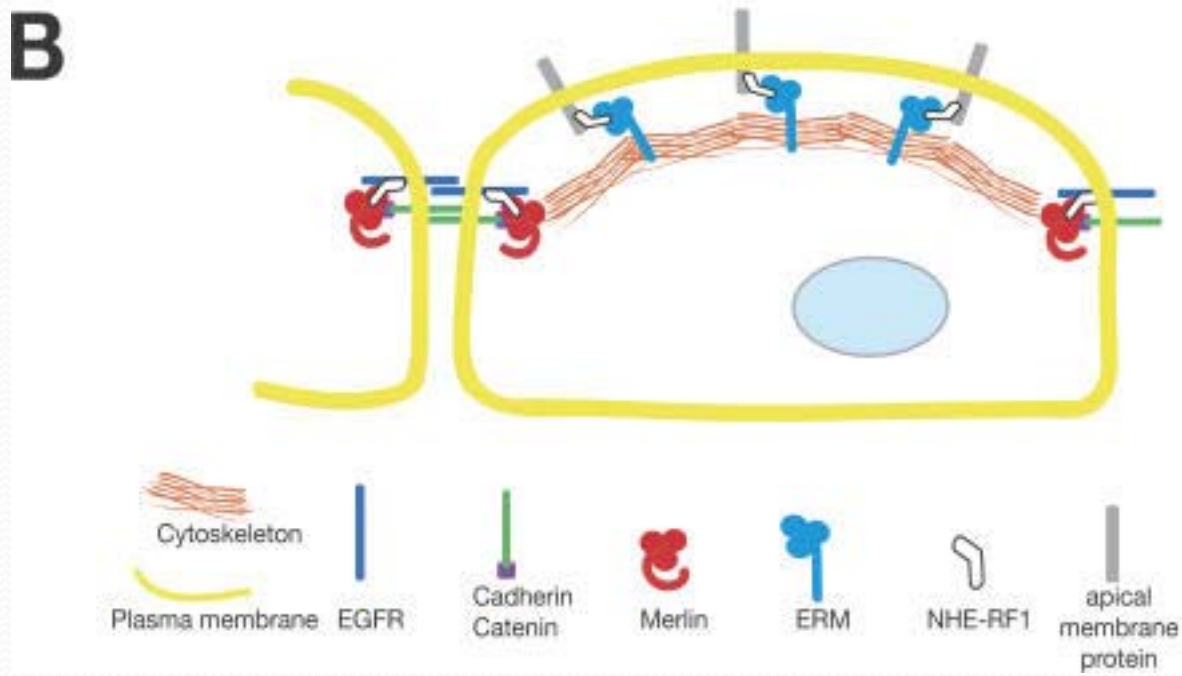
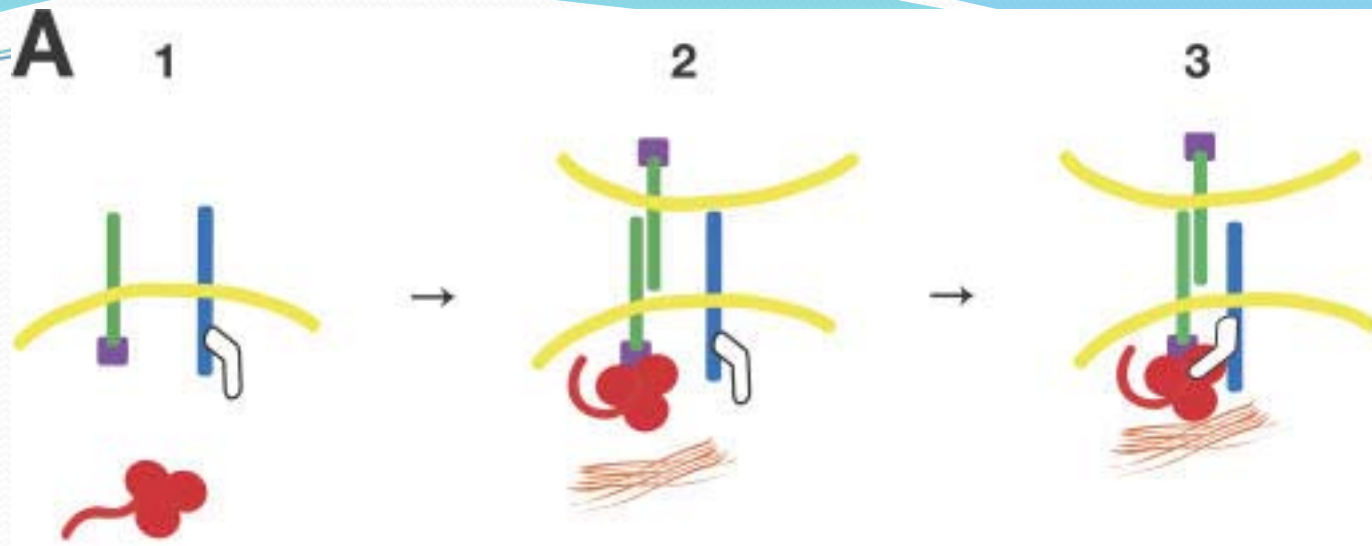
Perhaps surprisingly, knockout of these suppressors has little effect in normal cells indicating that they are redundant parts of larger networks that serve to constrain inappropriate proliferation.

## 6. Contact inhibition and evasion

Contacts formed between cells in dense 2D monolayers suppress proliferation in normal cells but not cancer cells. Suggests analogous systems operate *in-vivo* to ensure homeostasis.

Mechanisms obscure. Some insight from Merlin the neurofibromatosis 2 (NF2) gene product and tumor suppressor that couples E-cadherin to EGF receptor signaling thereby increasing cell-cell attachment and limiting EGF signaling.







## **7. Resisting cell death**

Apoptosis

Autophagy

Necrosis

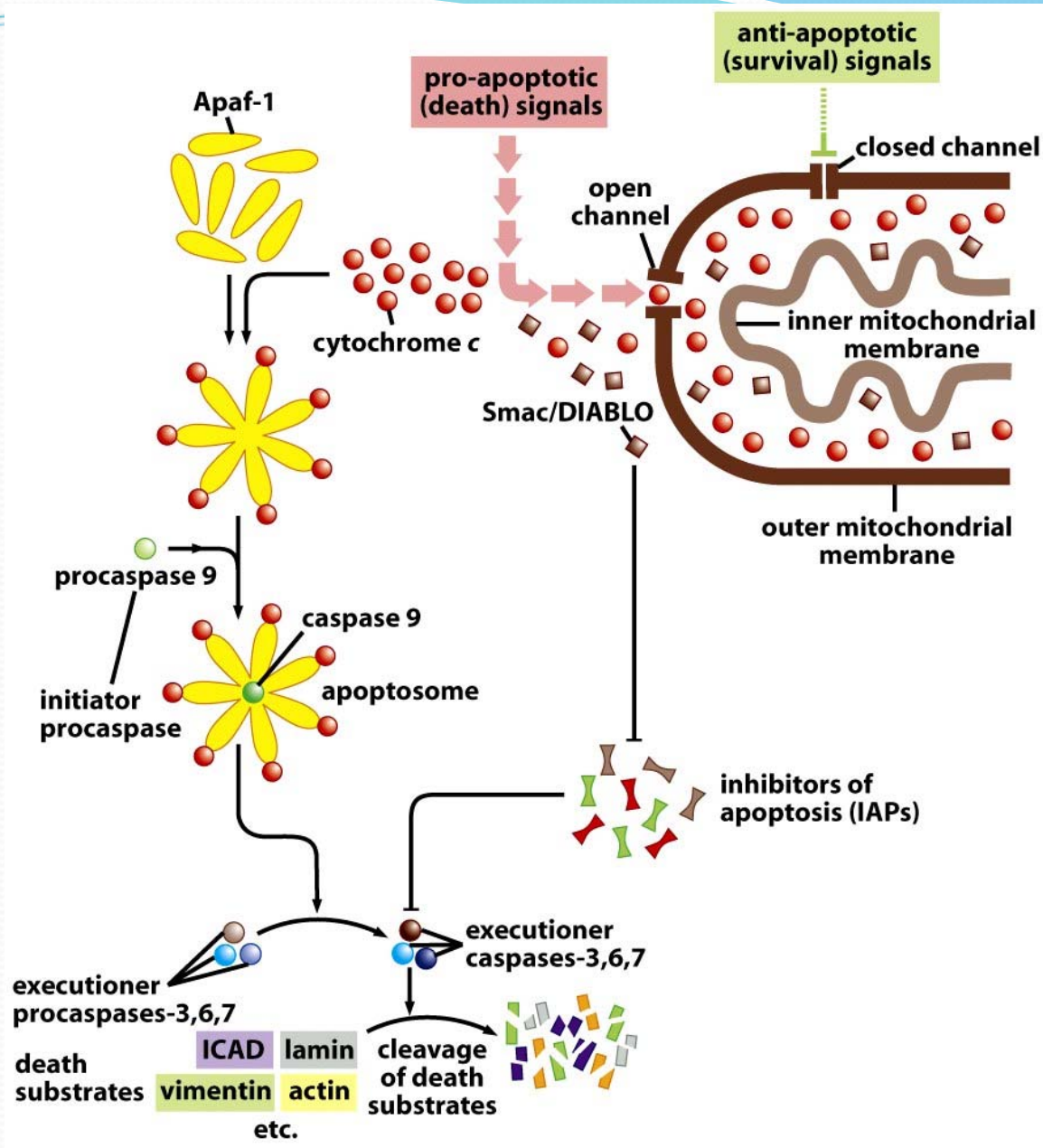


Figure 9-29 The Biology of Cancer (© Garland Science 2007)

# Anti-apoptotic strategies used by cancer cells

Pro-apoptotic proteins (blue) are decreased while anti-apoptotic proteins (red) are elevated.

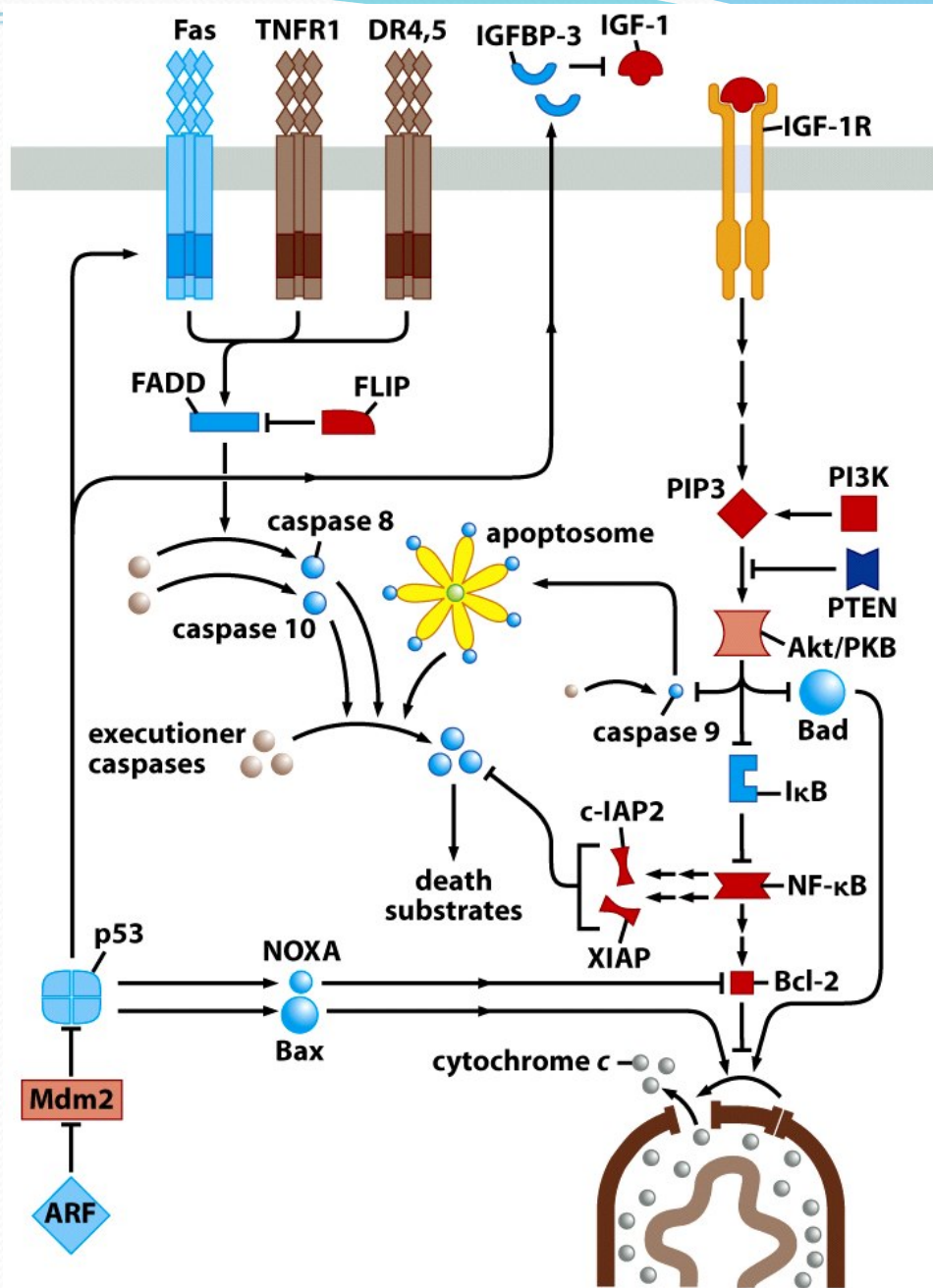


Figure 9-34 The Biology of Cancer (© Garland Science 2007)

## **8. Enabling replicative immortality**

Telomerase expression enhanced in transformed cells. Telomerase extends telomeric DNA thereby countering telomeric erosion associated with cell division.

By extending telomeres cancer cells avoid triggering senescence or apoptosis the two barriers to continued proliferation.

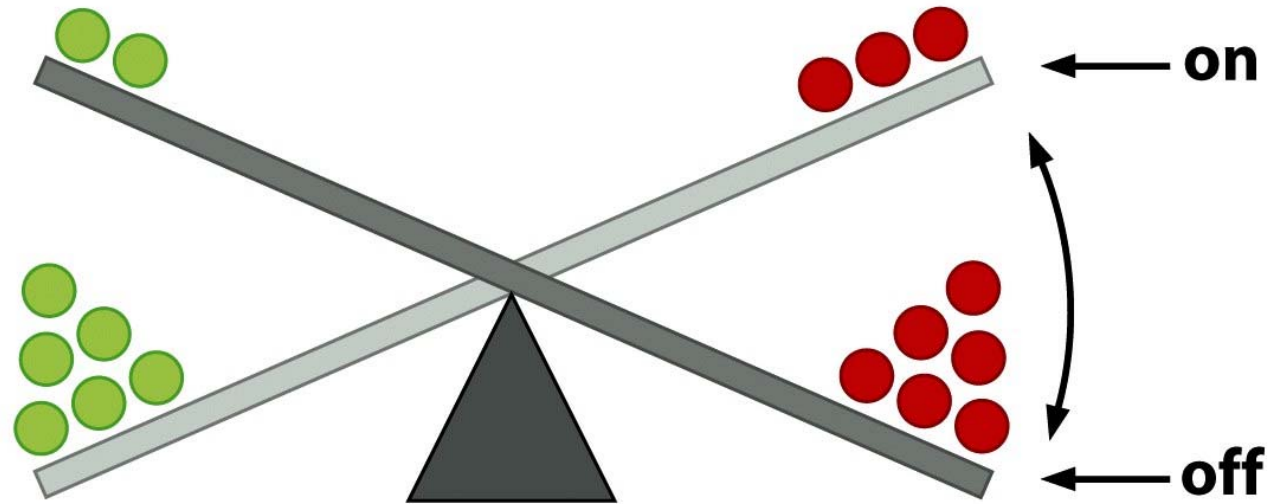
## **9. Inducing angiogenesis:**

Angiogenic switch

Gradations of switching

Vascular progenitor cells contribute to tumor angiogenesis.

## The angiogenic switch



● **activators**  
VEGF-A  
VEGF-B, -C  
FGF1 (aFGF)  
FGF2 (bFGF)  
other FGFs  
etc.

● **inhibitors**  
thrombospondin-1, -2  
interferon  $\alpha/\beta$   
angiostatin  
endostatin  
collagen IV fragments  
etc.

## **10. Activating invasion and metastasis**

Epithelial mesenchymal transition (EMT) program

Enables transformed cells to acquire the ability to invade, avoid apoptosis and metastasize.

Complexity of metastatic colonization.



# Epithelial mesenchymal transition

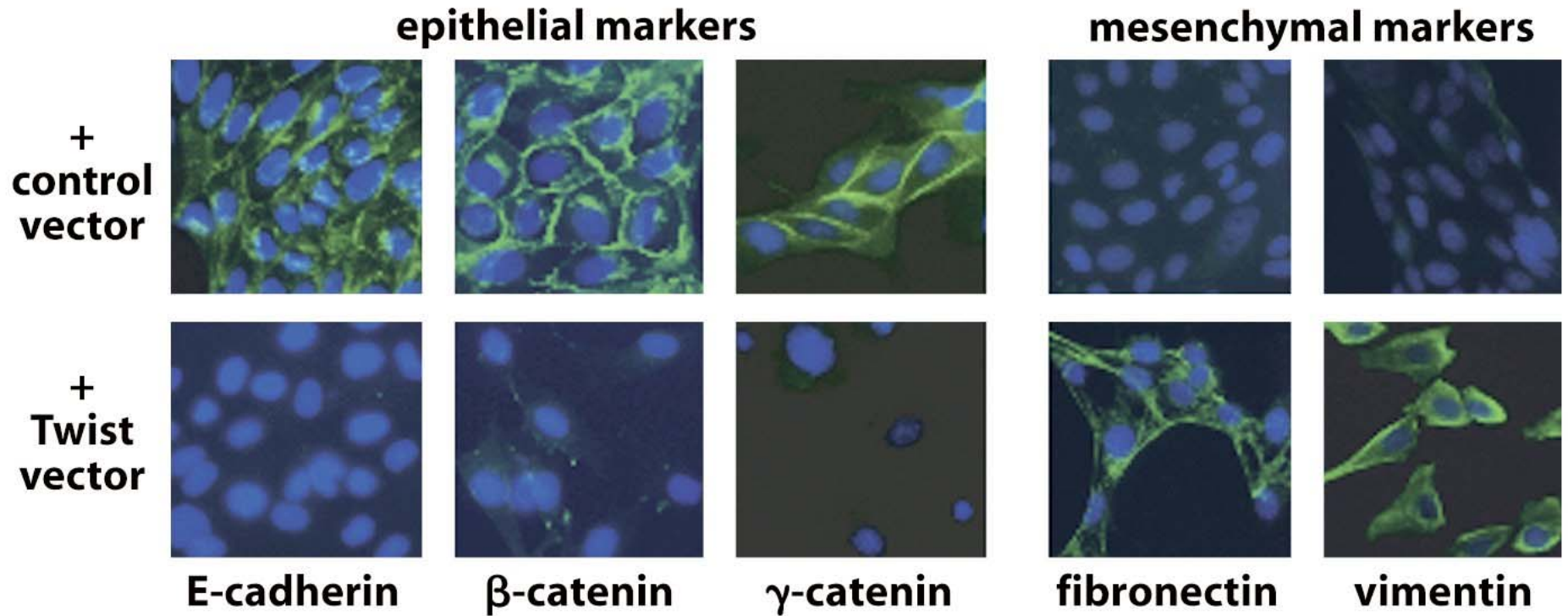
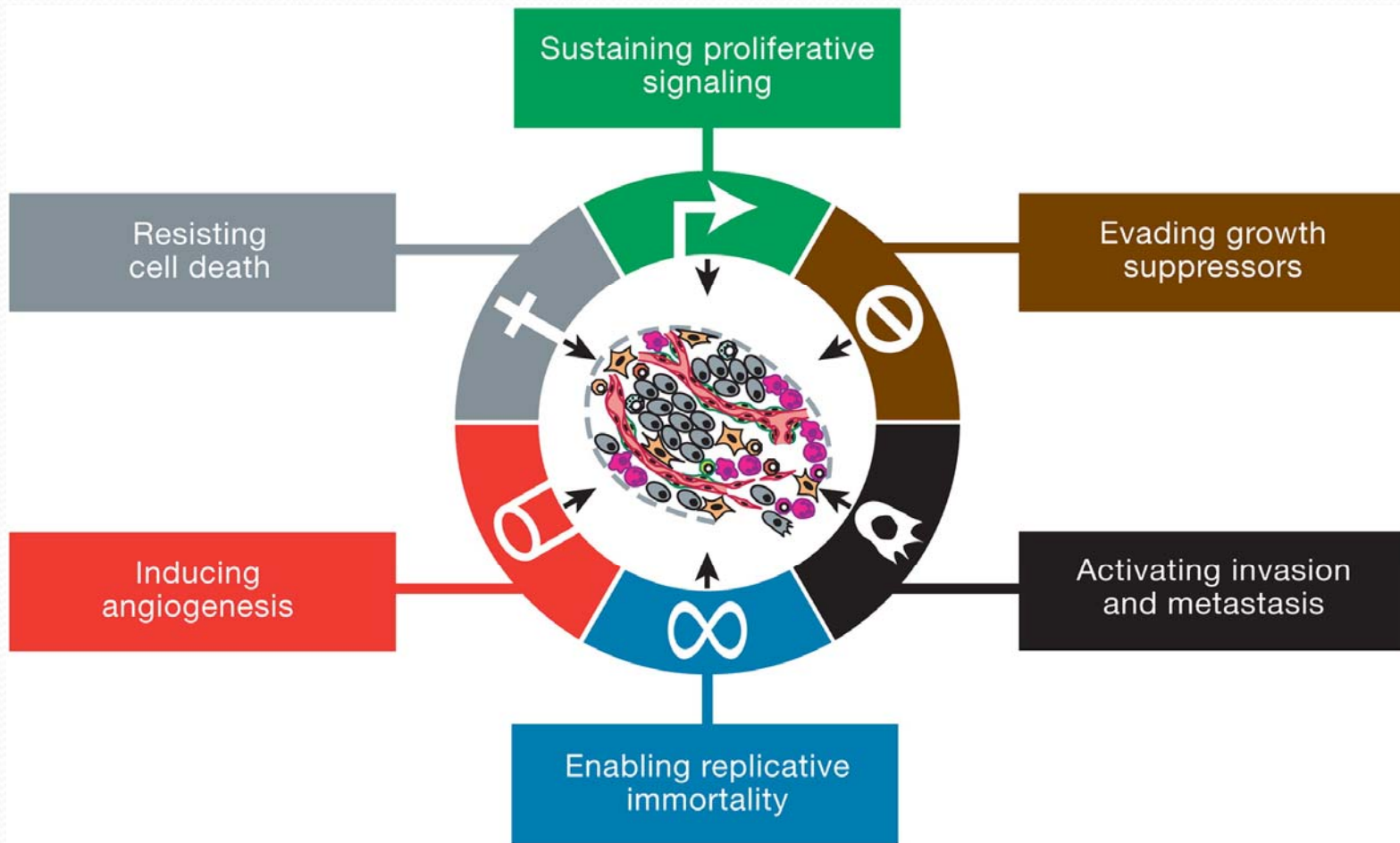


Figure 14-15a The Biology of Cancer (© Garland Science 2007)

## **11. Programming of hallmark capabilities by intracellular circuitry**

Signaling molecules that affect cancer cells operate as NODES in integrated circuits that are reprogrammed derivatives of circuits in normal cells.

Critical sub-circuits regulate hallmark capabilities.



Hallmarks of cancer: Hanahan and Weinberg 2000



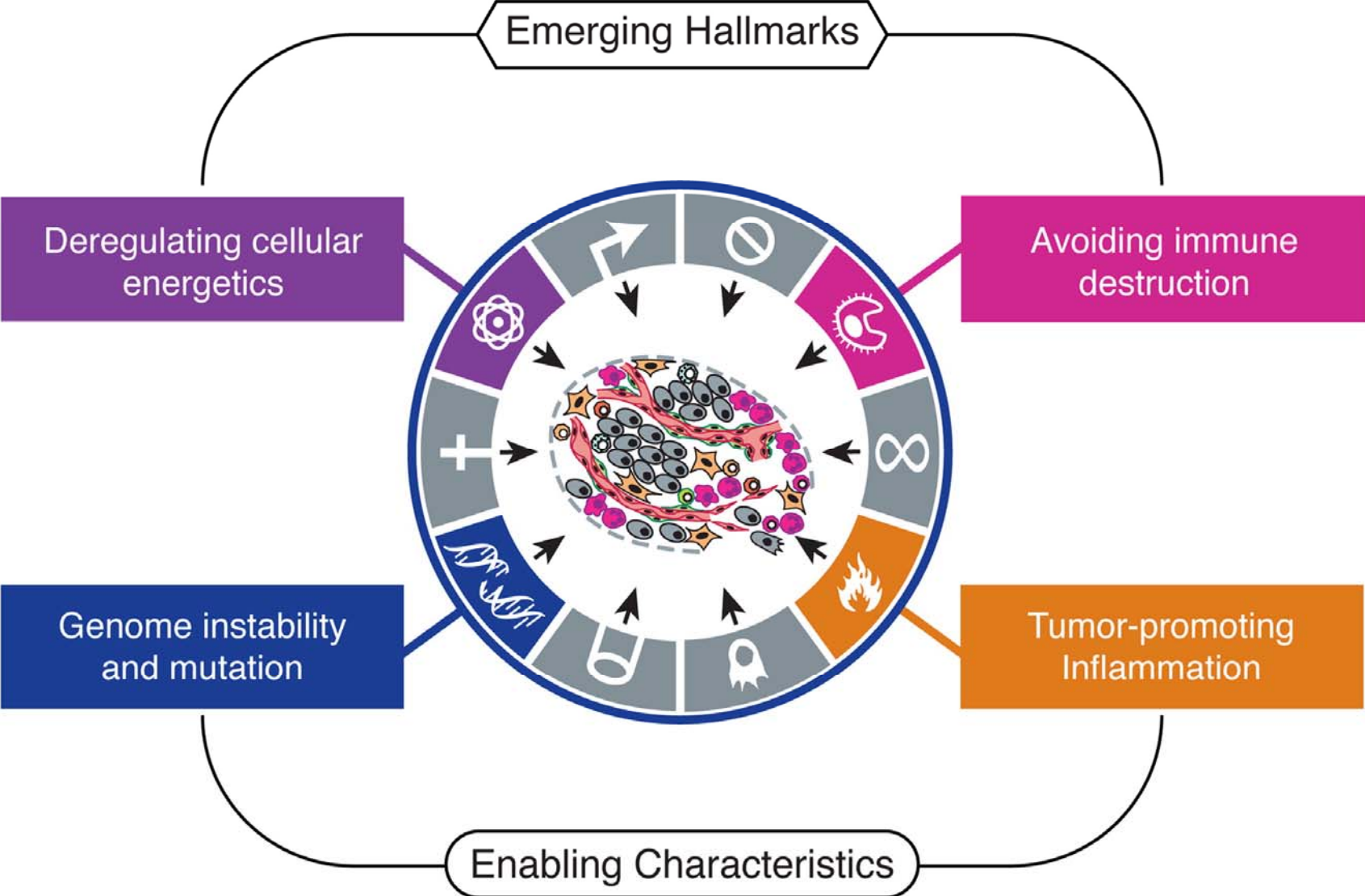
## **12. Enabling characteristics and emerging hallmarks**

Genome instability and mutation

Tumor-promoting inflammation

Reprogramming energy metabolism

Avoiding immune destruction





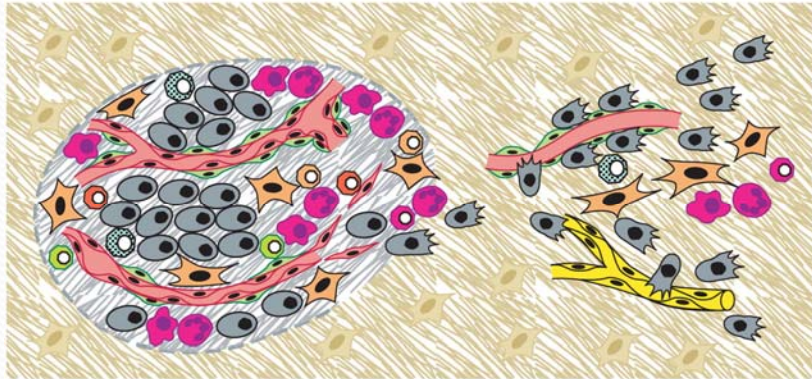
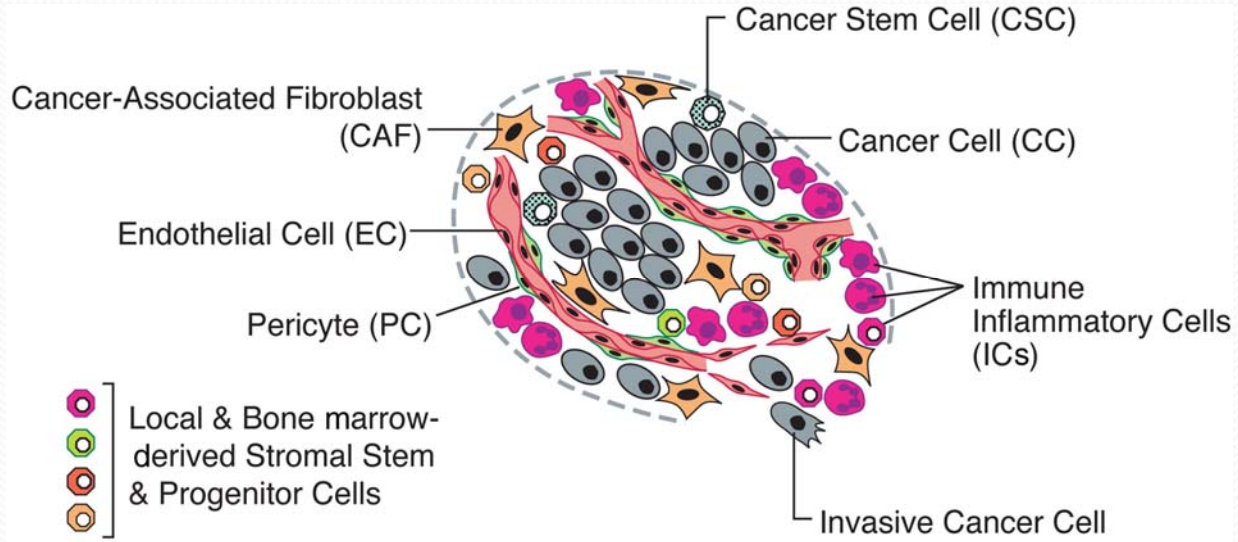
**Role of the tumor microenvironment:**

Cancer cells and cancer stem cells

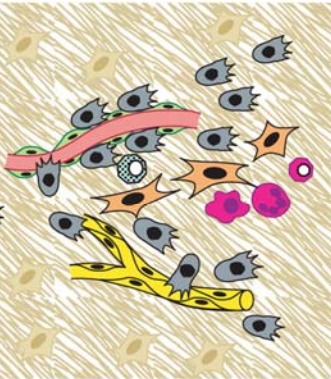
Endothelial cells

Inflammatory cells

Stem and progenitors in the stroma



Core of Primary Tumor microenvironment



Invasive Tumor microenvironment



Metastatic Tumor microenvironment

Cancer may be a disease of stem cells

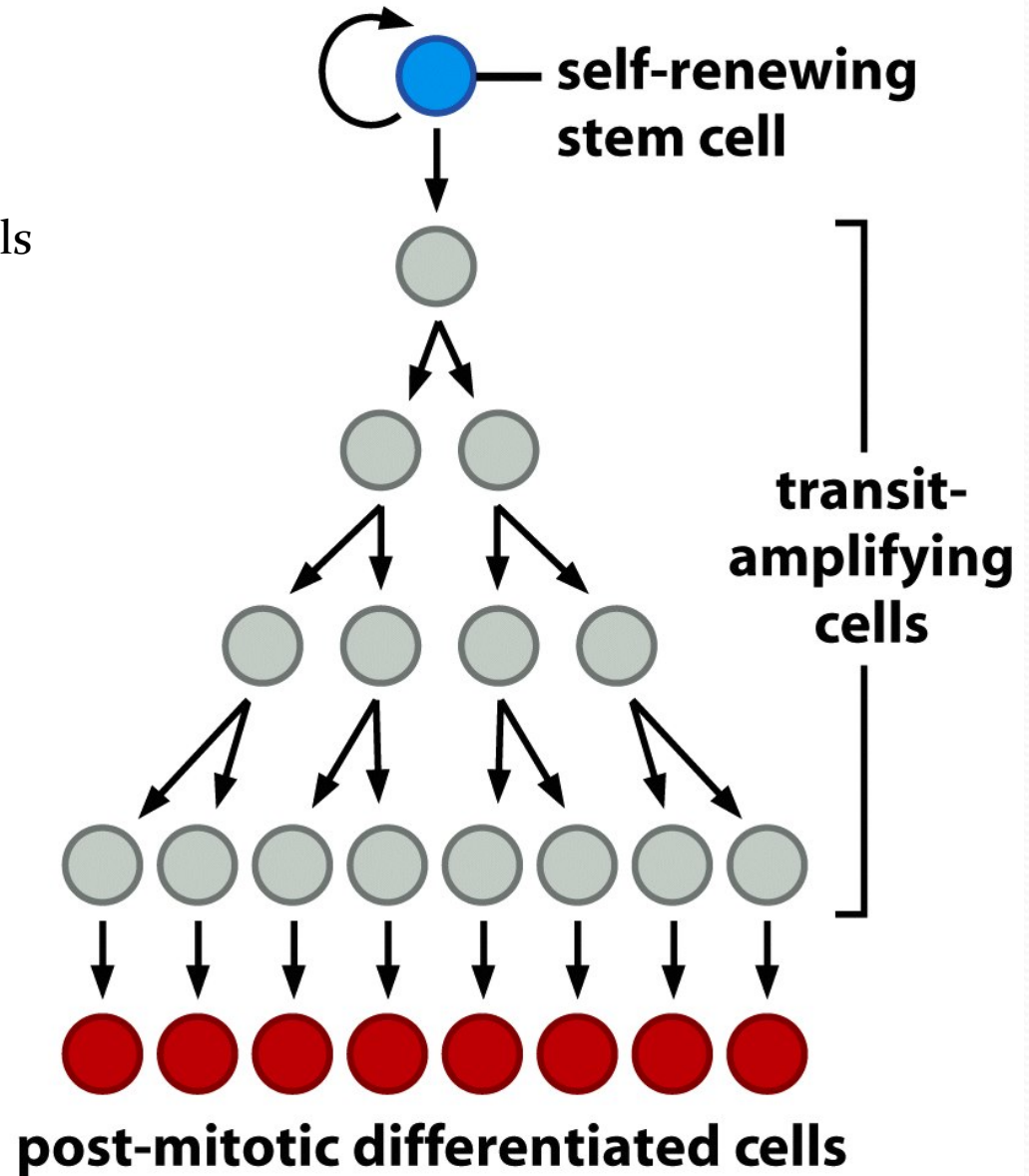


Figure 11-16b The Biology of Cancer (© Garland Science 2007)



## **Central question:**

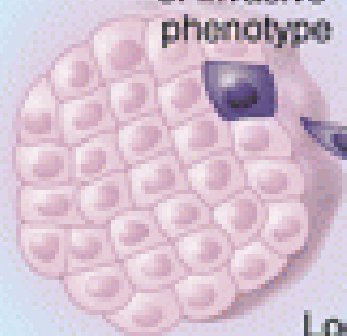
Does acquisition of malignant traits occur as an almost inevitable consequence of primary tumor progression or as an accidental by-product?

If primary tumors arise through acquisition of a sequence of genetic and epigenetic alterations each of which confers increased fitness to proliferate (in a Darwinian sense) then how does acquisition of invasiveness and metastatic dissemination reflect selection within the primary tumor?

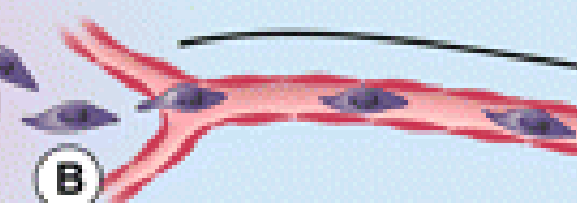
Either these traits are selected because they provide an advantage within the primary OR these traits (almost) accidentally confer the ability to respond to contextual signals that induce them to express highly malignant traits.

## Physical translocation from primary tumor to distant organ

**A** Acquisition  
of invasive  
phenotype



**B** Local invasion  
cells invade into surrounding  
stroma, then intravasate to enter  
hematogenous circulation



**C** CTCs transit to  
distant organ

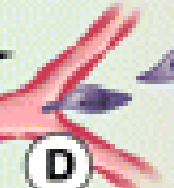


## Colonization

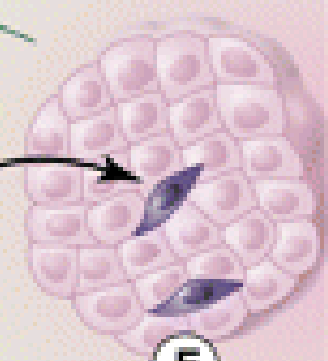
**E** Survival at  
secondary site





**D** CTCs extravasate  
and invade into the  
parenchyma of  
foreign tissue



**F** Adaptation and  
proliferation to  
form metastases




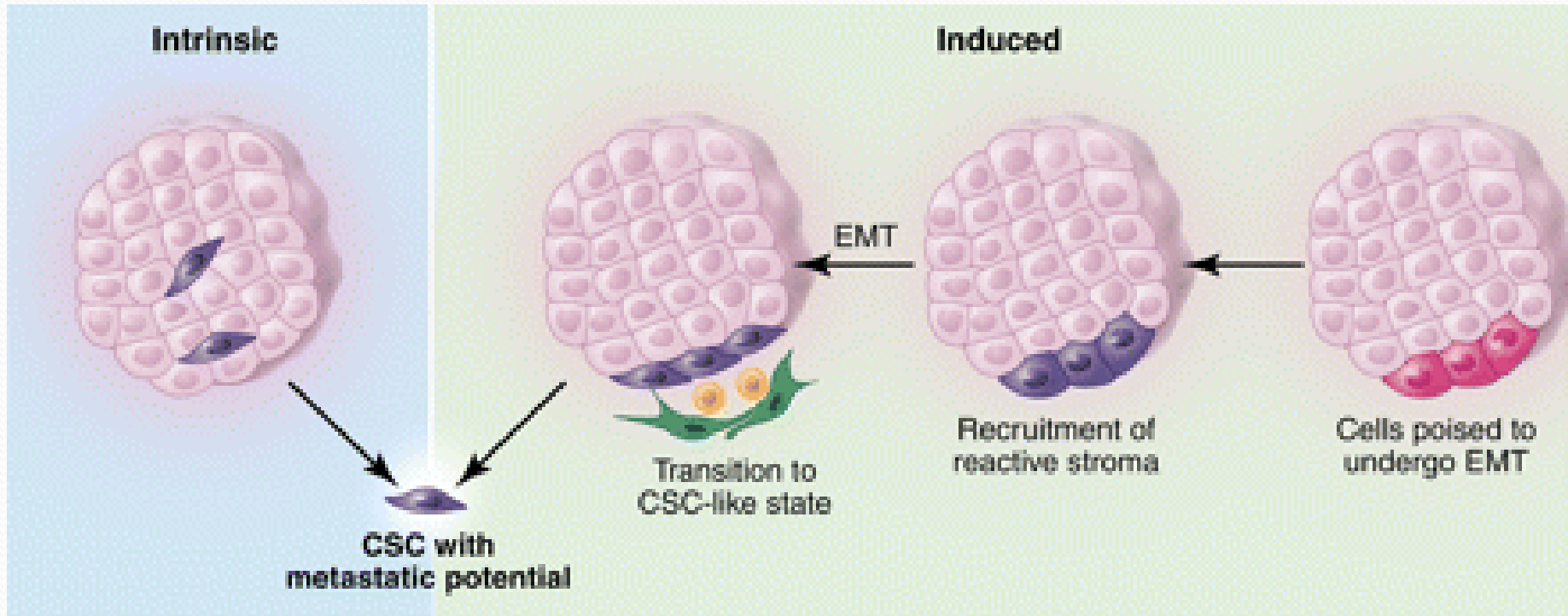
 Differentiated  
cancer cell







 Transitioning  
cancer cell

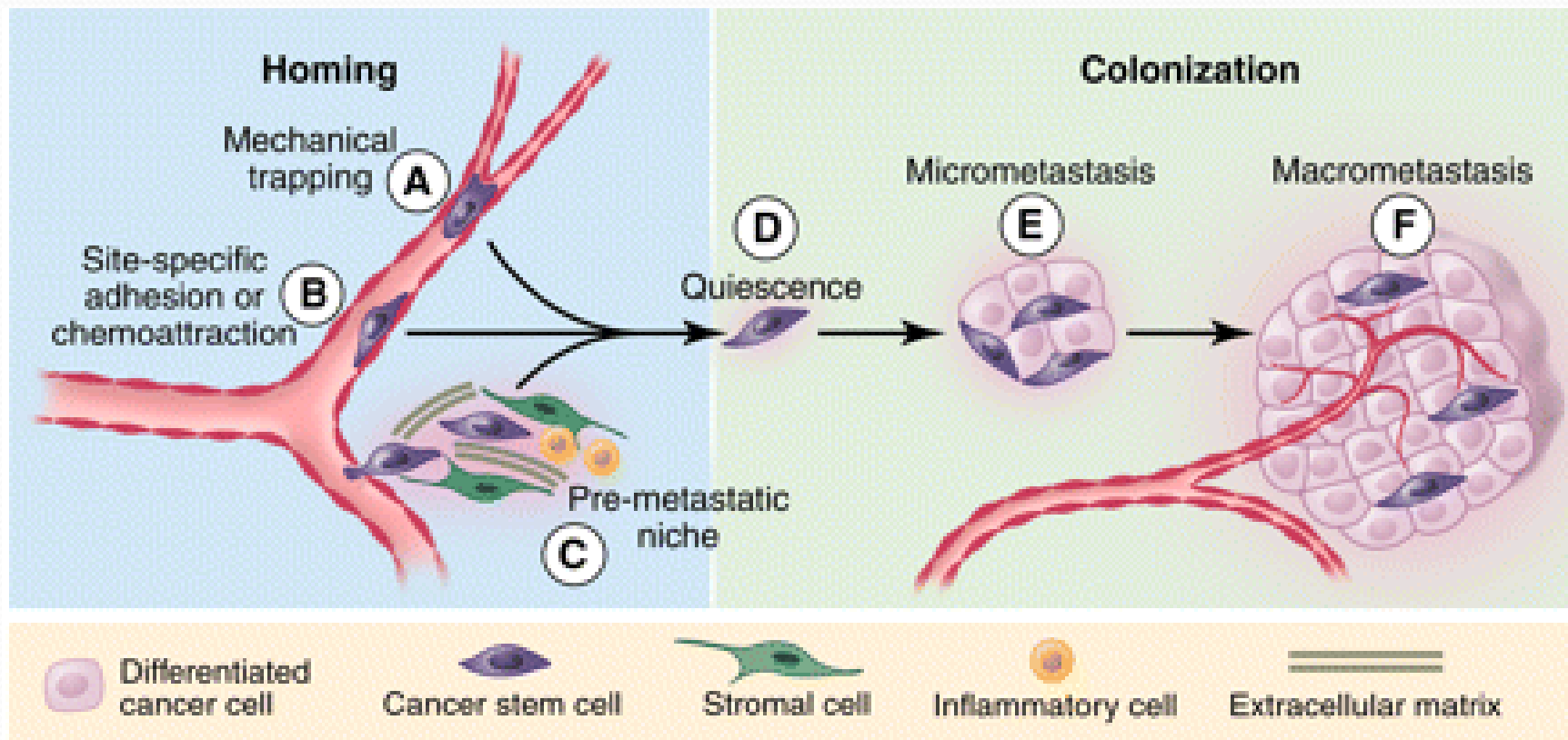
 Cancer  
stem cell

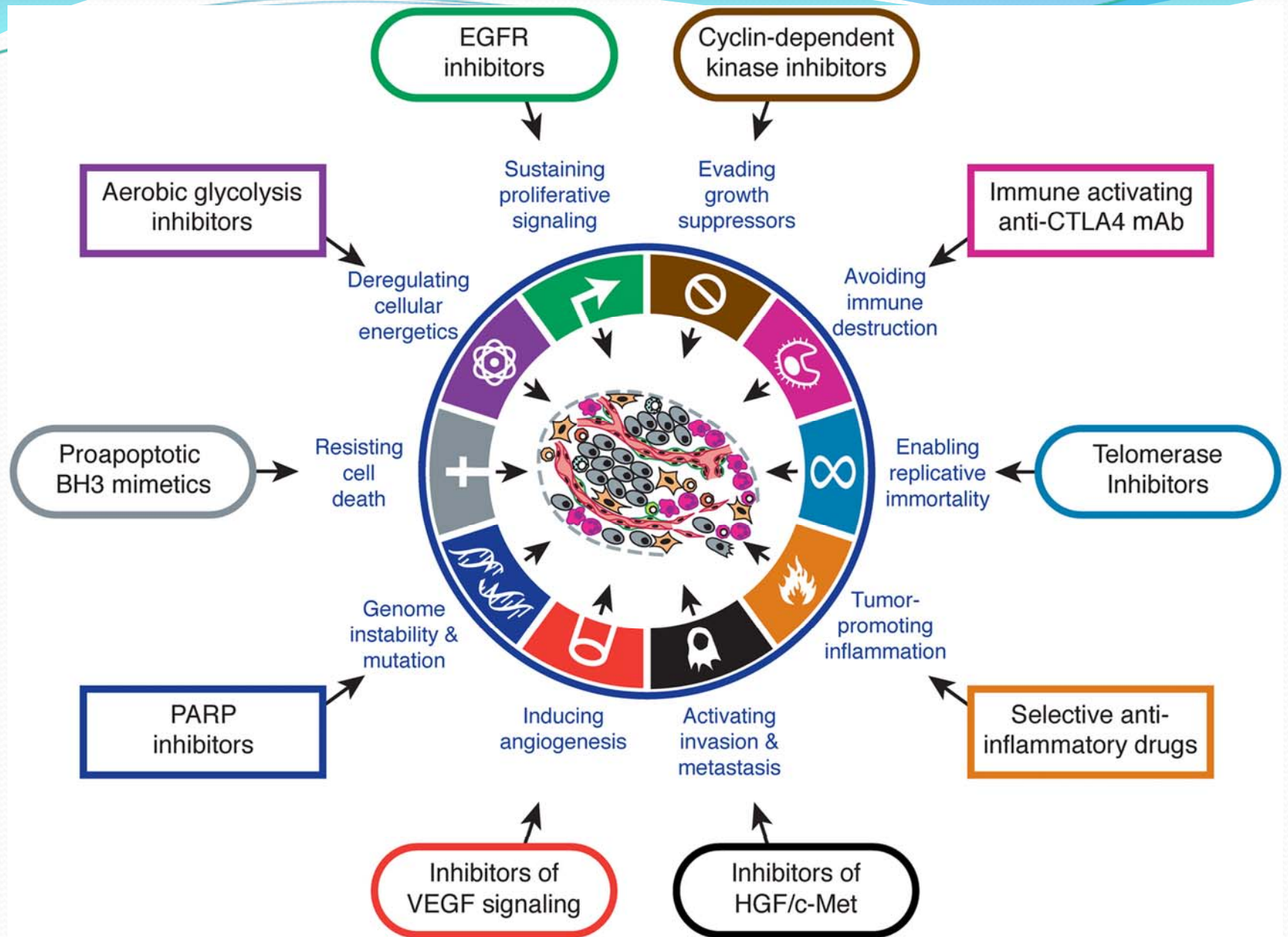
 Stromal cell

 Inflammatory cell



					
Differentiated cancer cell	Responsive differentiated cancer cell	Transitioning cancer cell	Cancer stem cell	Stromal cell	Inflammatory cell







**Texts:**

Weinberg The Biology of Cancer (chapters 1 and 2)

Hallmarks of cancer: the next generation Hanahan and Weinberg  
Cell 144: 646-674 2011

A perspective on cancer cell metastasis: Chaffer and Weinberg  
Science 331: 1559-1564 2011