

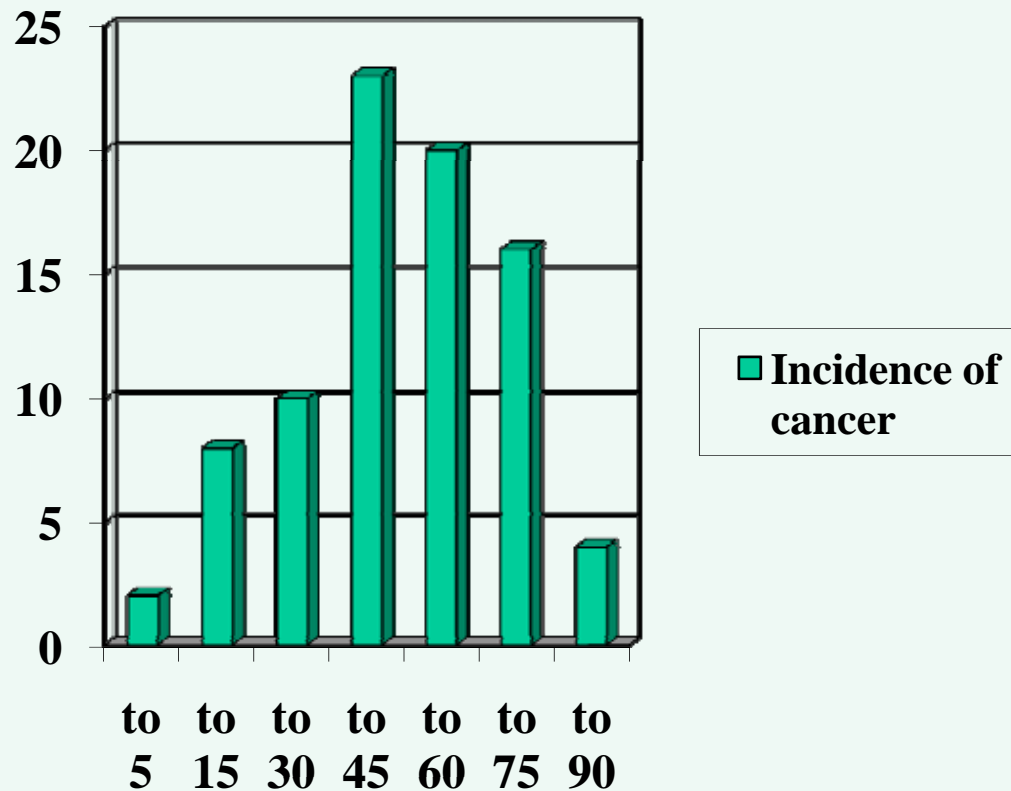
# Cancer and Oncogenes Bioscience in the 21<sup>st</sup> Century

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December 1, 2010

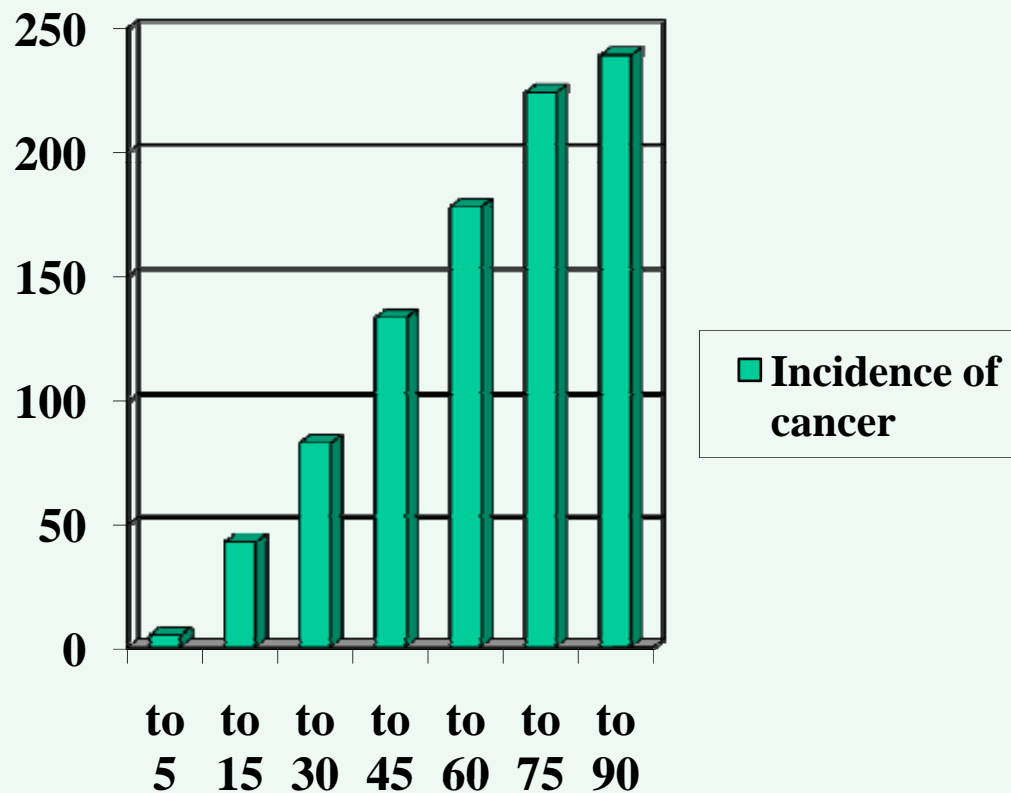
- Just a Few Numbers
- Becoming Cancer
- Genetic Defects
- Drugs

# Our friends and family



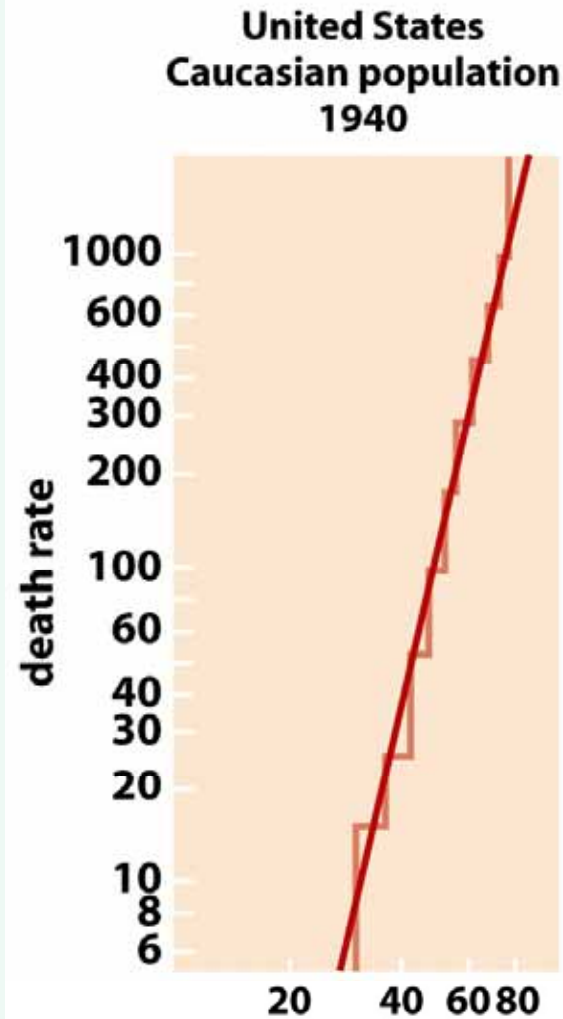
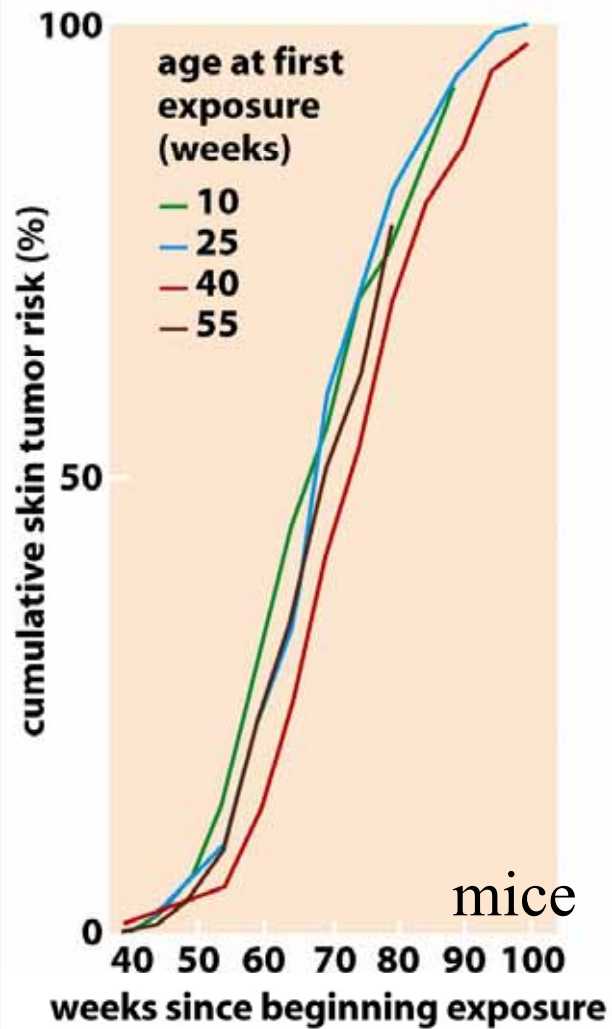
- More mutations as you get older
- More DNA damage due to environment
- One mutation can lead to others

# Data from 2009



- More mutations as you get older
- More DNA damage due to environment
- One mutation can lead to others

# Other similar data



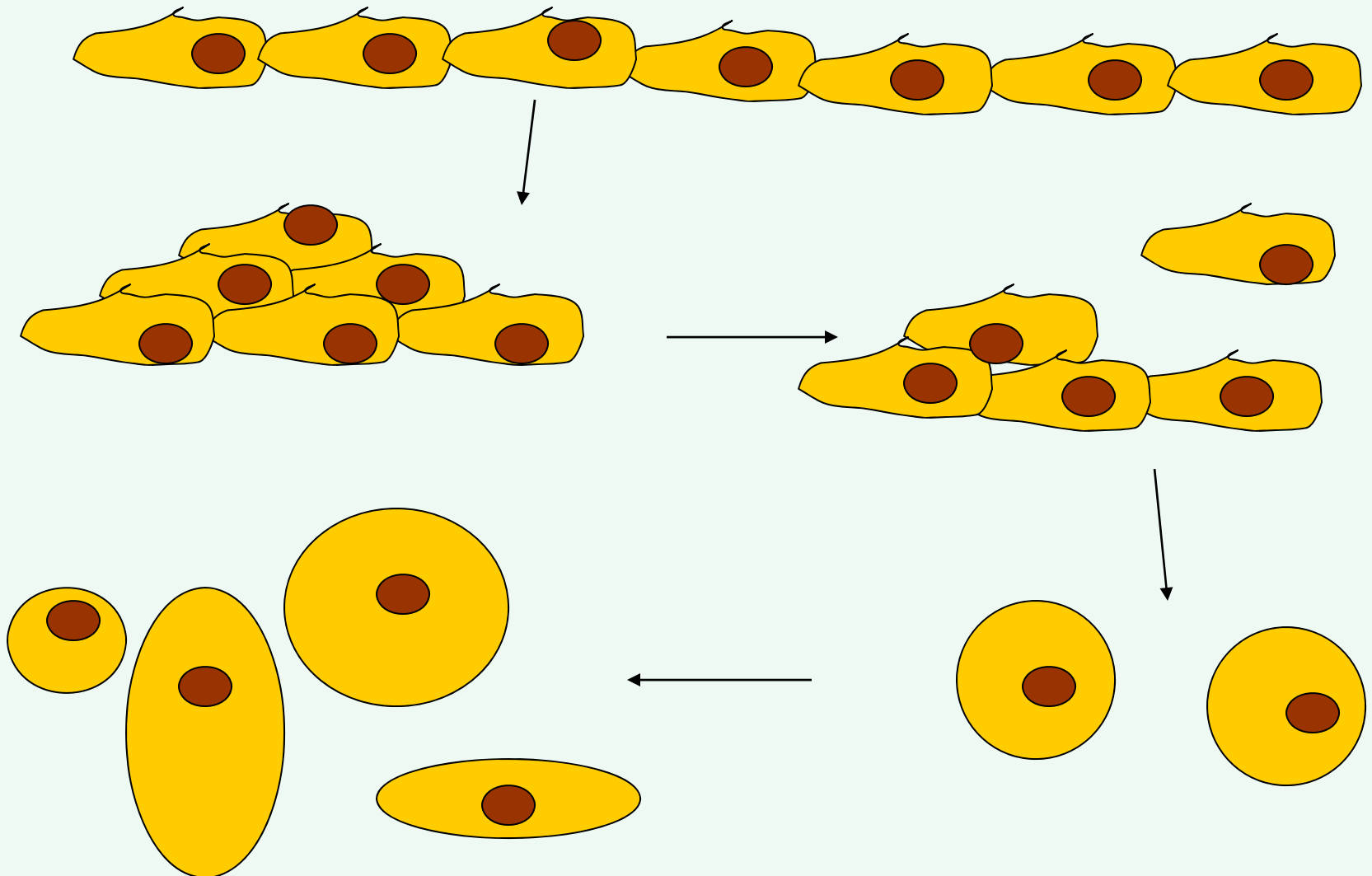
Weinberg, the Biology of Cancer

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

# Required characteristics

- Original hypothesis – 2 mutations, one in signaling and one in the nucleus.
- Statistical analysis says more like 5 or 6 mutations probably contribute to cancer.
- Typically at least one mutation is in a proliferation pathway.
- Benign → cancer requires at least one additional mutation.

# Evolution of a cancer cell

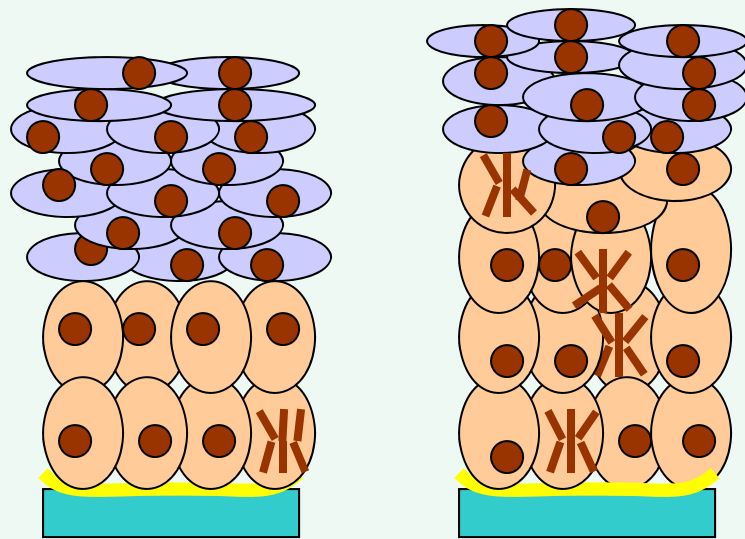


# Abilities acquired

- Grow rapidly
- Dissociate from neighboring cells
- Invade adjacent tissue
- Invade blood vessels or lymphatic system
- Escape immune system
- Arrest in a new location
- Get into target tissue
- Proliferate in new location



# Normal      Dysplasia



Pre-malignant,  
appear abnormal

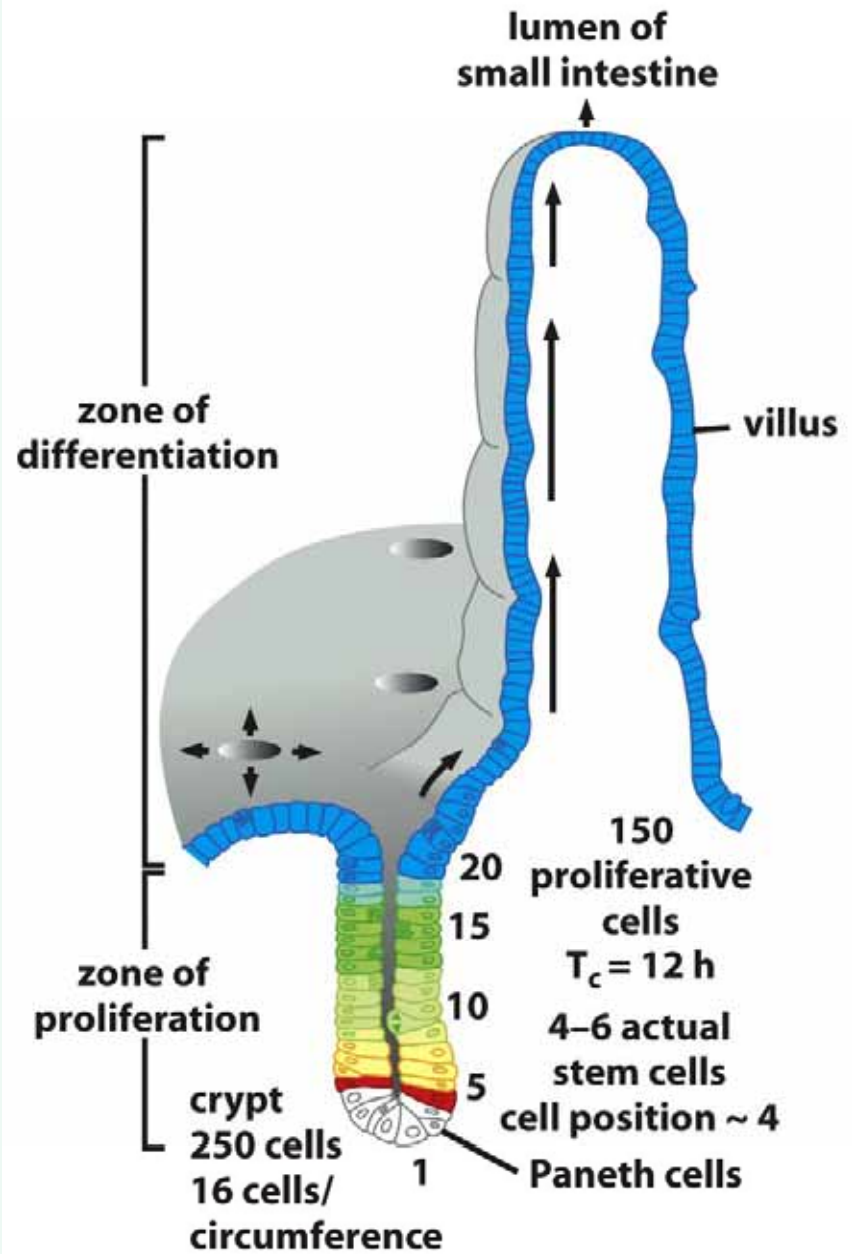
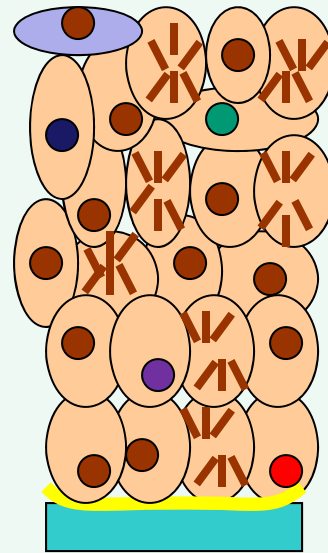


Figure 12-2a The Biology of Cancer (© Garland Science 2007)

# Carcinoma

Increased cell proliferation

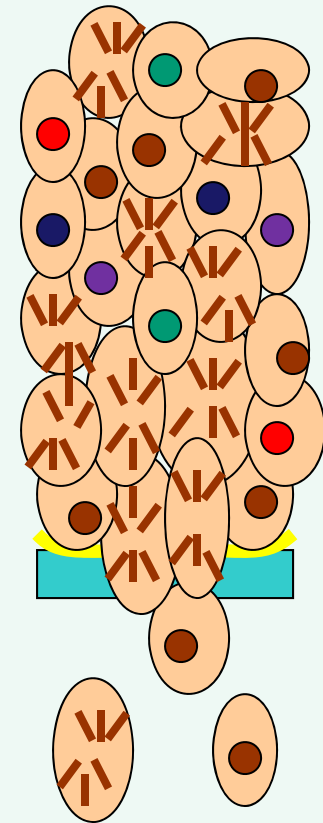
Additional possible changes here include decreased ability to catch mistakes



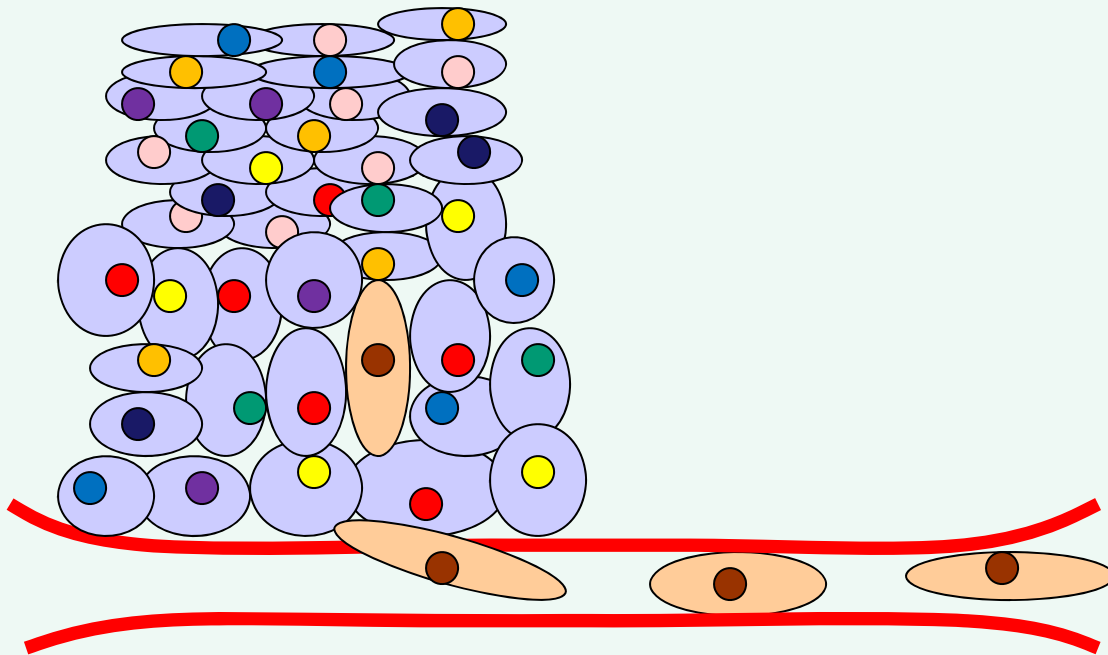
# Malignant

Epithelial to  
mesenchymal transition.

Cells are able to change  
characteristics and gain  
the ability to migrate  
across barriers or  
through membranes.



# Extravasation



Blood vessels are recruited for nutrient delivery.

# One pathway

Normal Epithelium



Hyperplastic epithelium



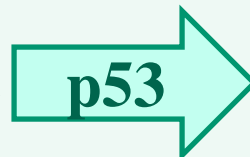
Intermediate Adenoma



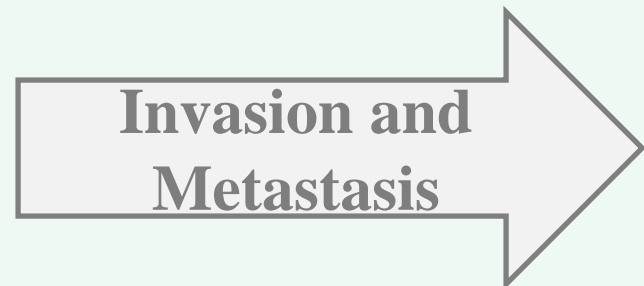
Early Adenoma



Late Adenoma



Carcinoma



# Colon cancer genes (APC)

- APC > 70%
  - Binds  $\beta$ -catenin – Colon cell differentiation
- kRas ~ 50%
  - Activation of signals for growth
- DCC > 70%
  - Cell-cell adhesion
- p53 > 70%
  - Lots of changes allowed - carcinoma
- smad4 ~ 20%
  - Transcription factor – gene expression

# Many pathways

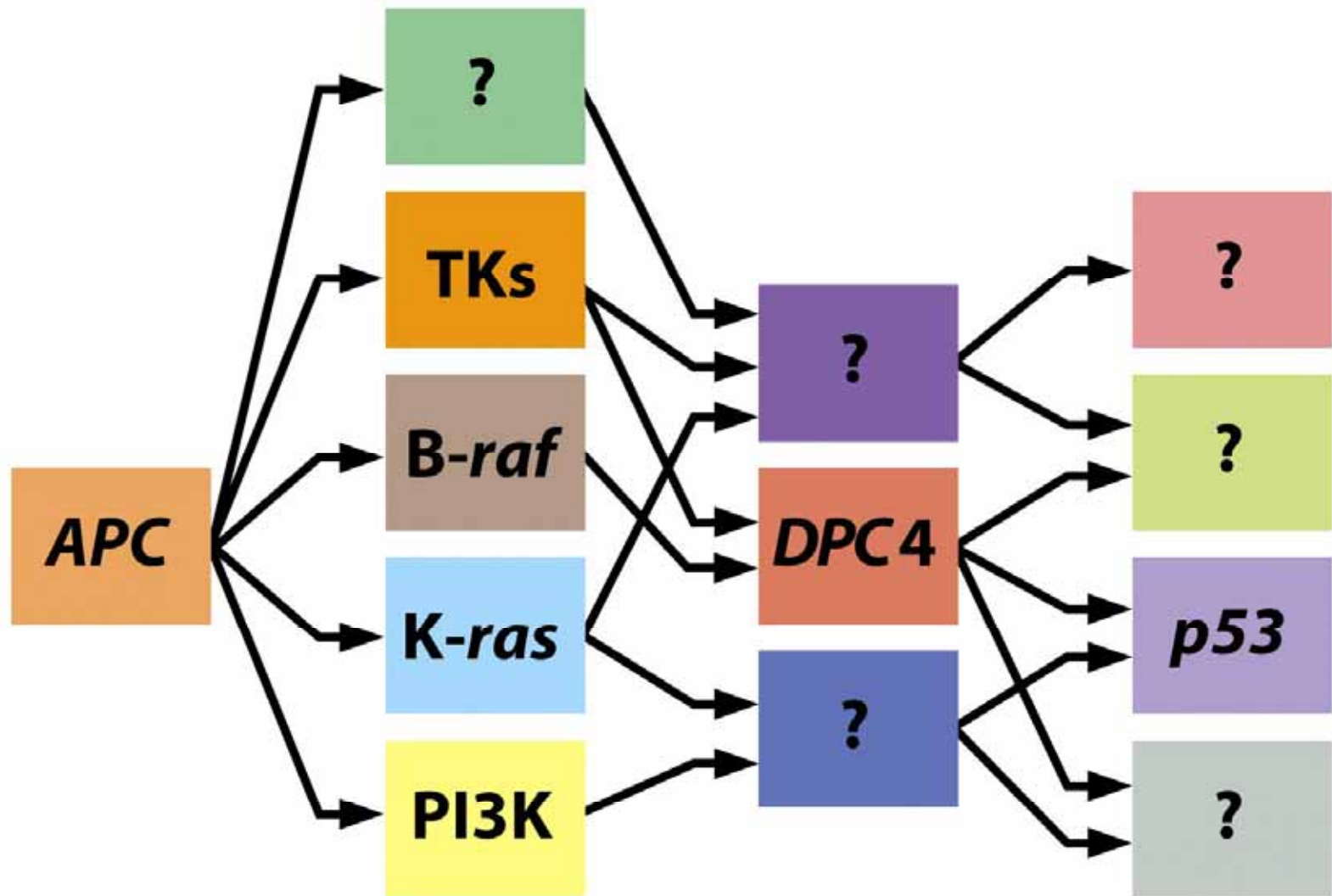


Figure 11-11a The Biology of Cancer (© Garland Science 2007)

# Two ways to change

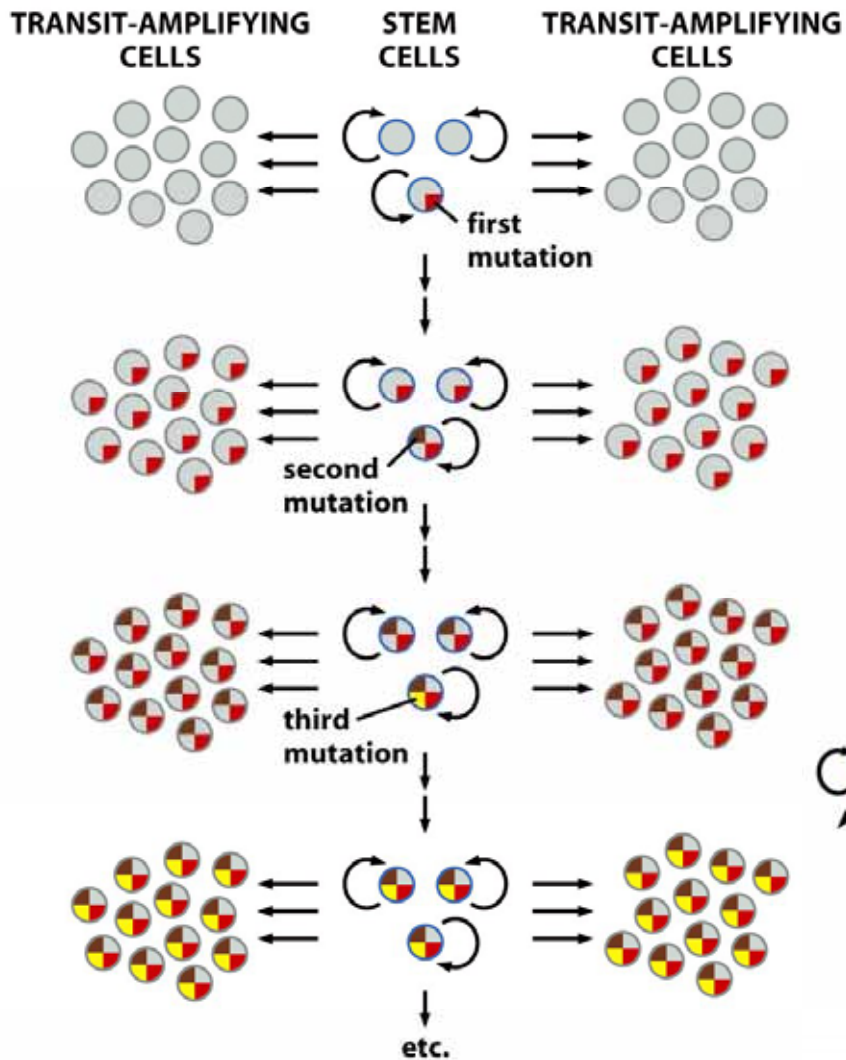


Figure 11-17 The Biology of Cancer (© Garland Science 2007)

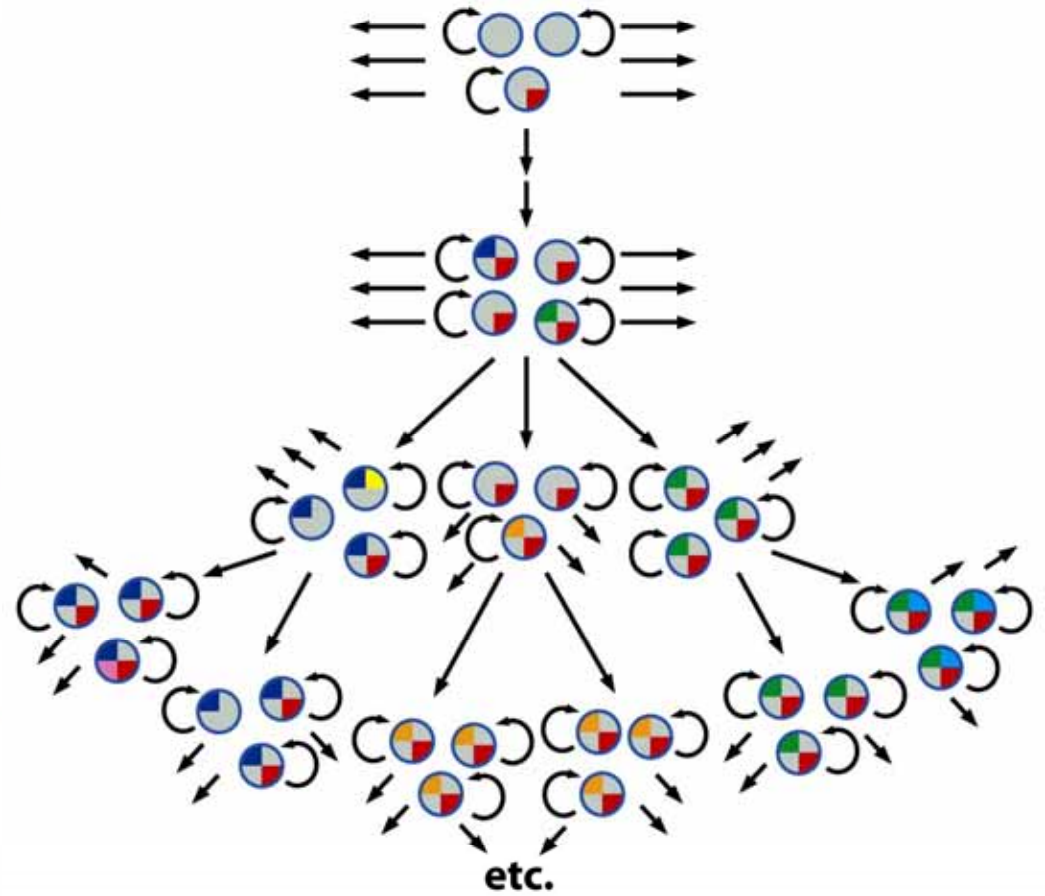


Figure 11-18 The Biology of Cancer (© Garland Science 2007)



# Reactive oxygen species damage DNA

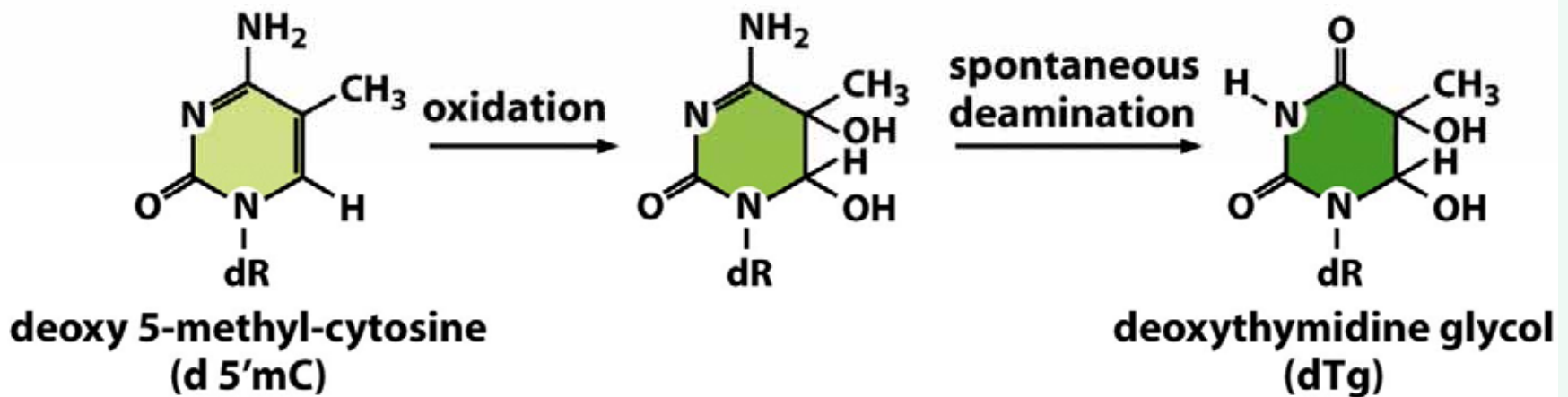
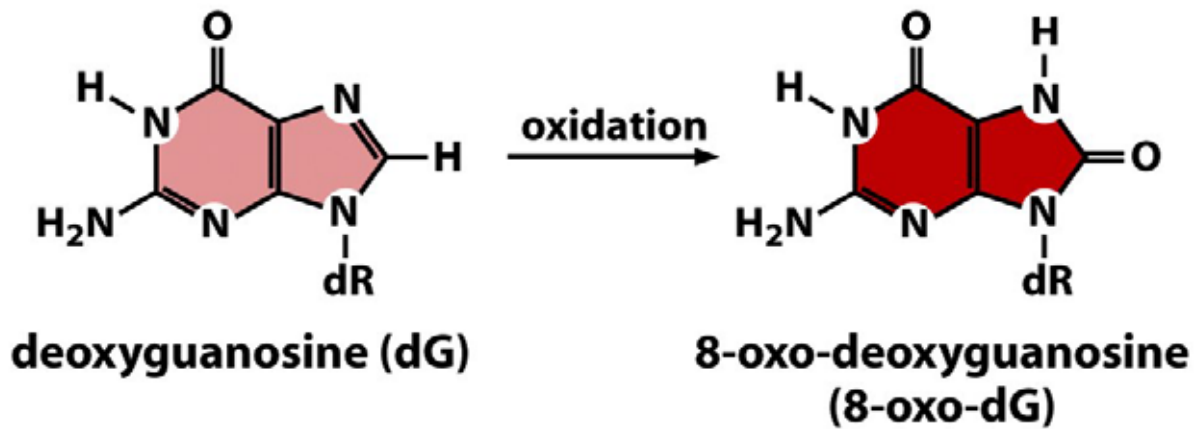
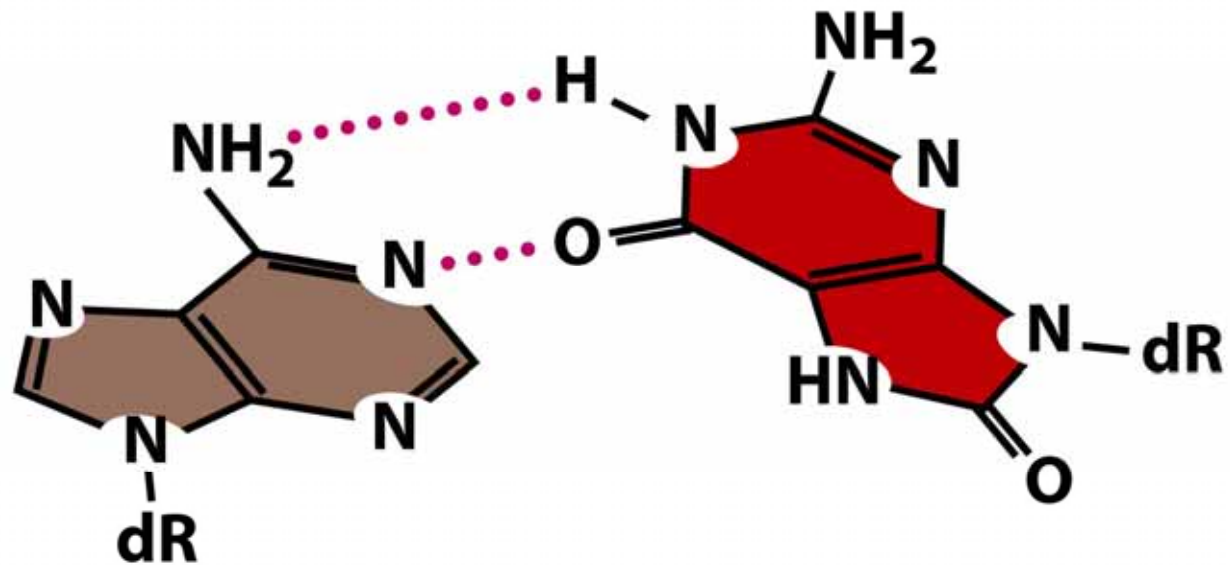


Figure 12-12a The Biology of Cancer (© Garland Science 2007)

# Damage outcomes



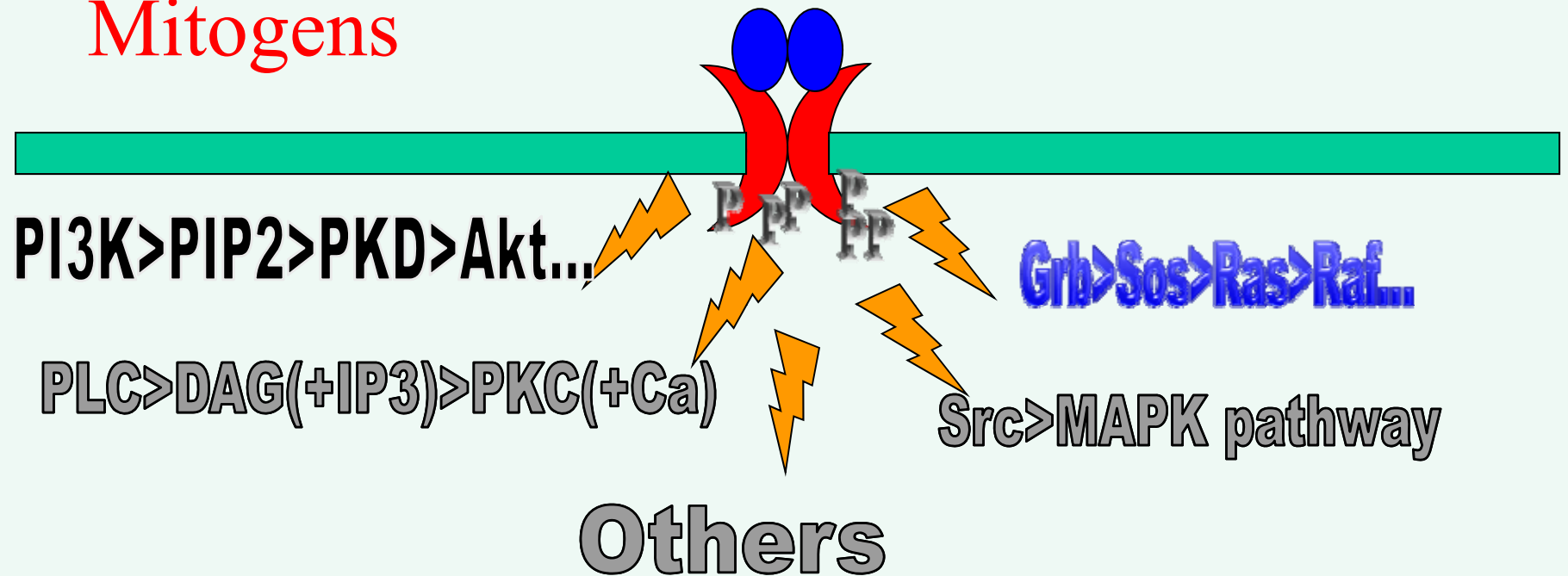
**mispairing of 8-oxo-dG  
with deoxyadenosine (dA)**

# But repair enzymes fix most problems

- If you cannot fix the all of the DNA damage, mistakes accumulate more rapidly and cancer usually starts earlier.
- An example is individuals with Li-Fraumeni syndrome whose cells do not recognize damage (faulty p53).
- Another example is Xeroderma Pigmentosum, where patients cannot repair UV damage and get skin cancer more rapidly than most people – with much less exposure

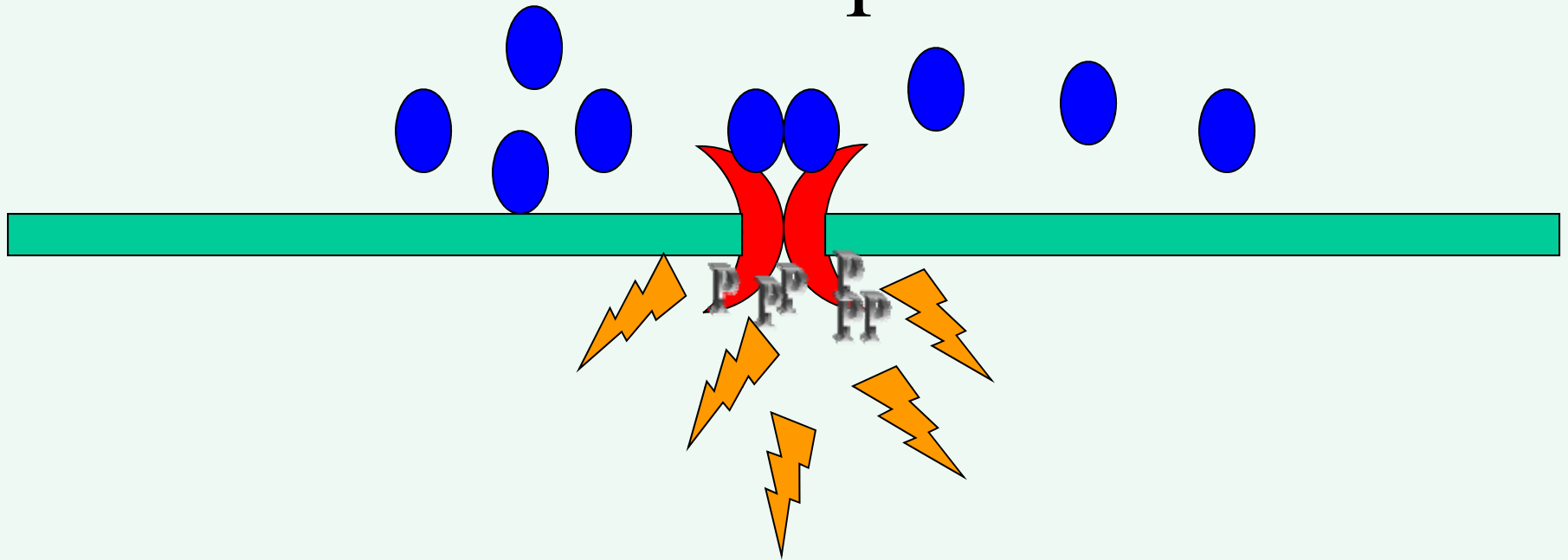
# Growth factors and the cell cycle

## Mitogens



Together these pathways result in a complicated plan that results in a balance of proteins and other factors leading to cell growth and division.

# SCF is over produced



In many Small Cell Lung Carcinoma patients, lots of SCF (stem cell factor) is produced and the cells also contain the growth factor receptor for this molecule. Therefore, continuous growth signaling occurs.

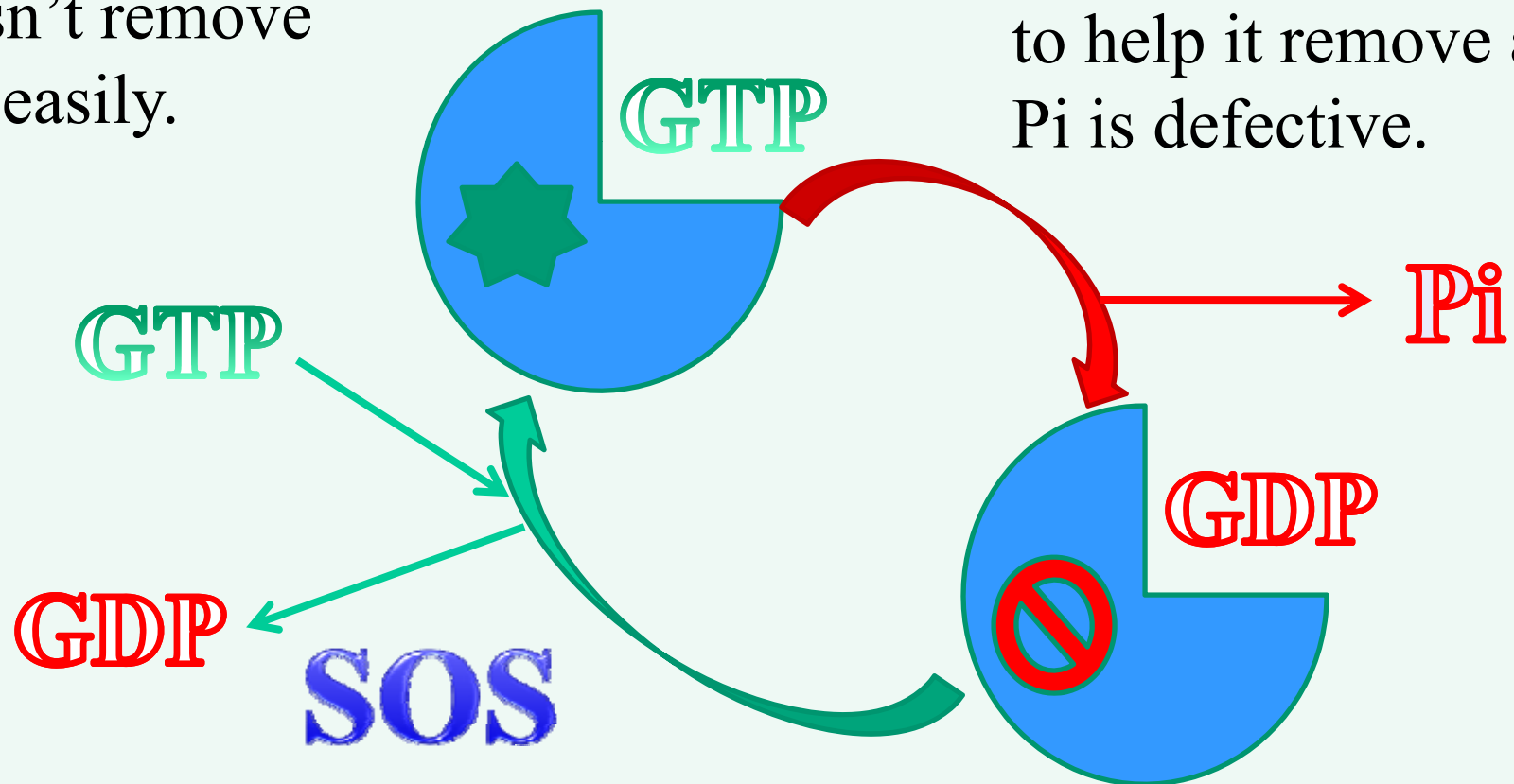
# Ras signaling and cancer



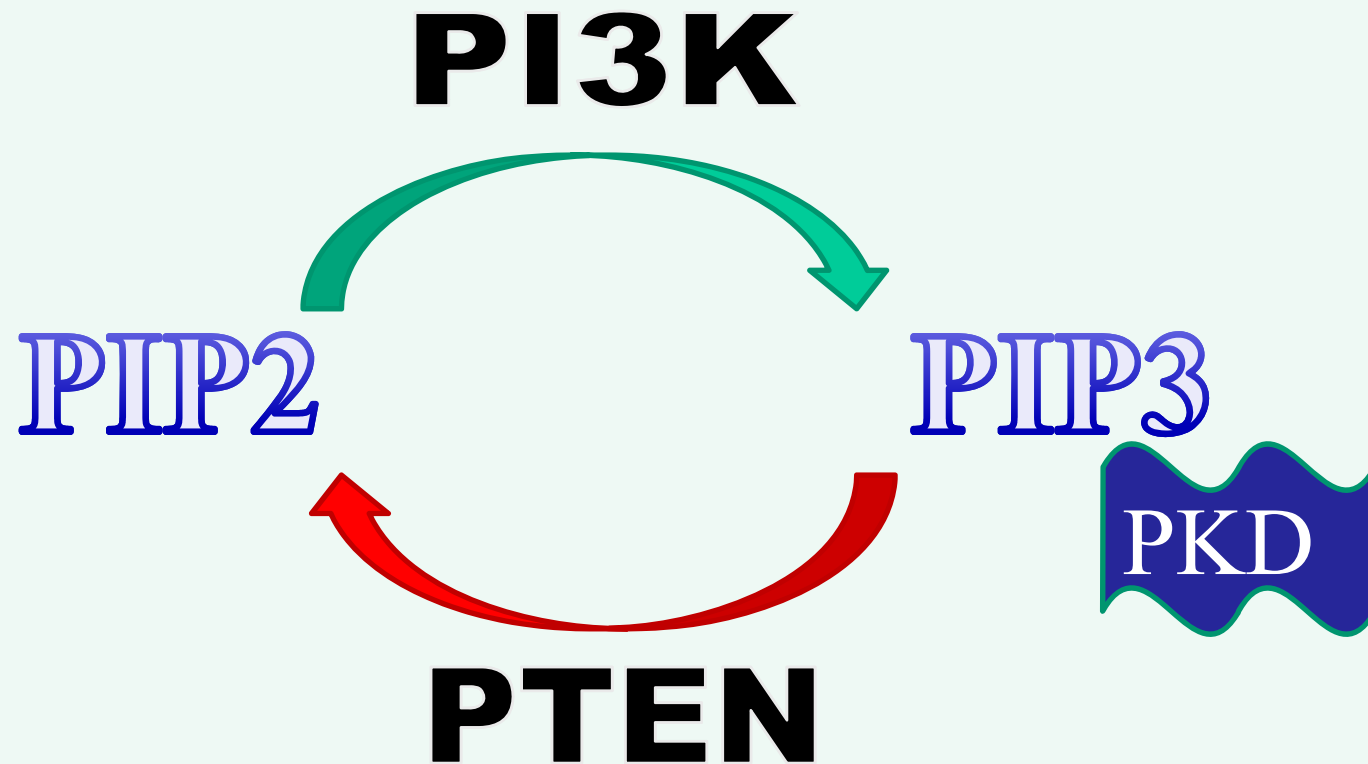
# Ras (a G protein)

Mutant Ras  
doesn't remove  
a Pi easily.

A protein that  
associates with Ras  
to help it remove a  
Pi is defective.



**PI3K>PIP2>PKD>Akt...**





# Types of genes that get mutated

- Oncogenes – gain of function
  - Hybrid proteins that change function
  - Over-production of a protein
  - Activity increases
  - **CANCER ONLY NEEDS ONE BAD COPY**
- Suppressor – loss of function
  - They can't check growth
  - **USUALLY YOU LOSE BOTH GENES** if there is a defect leading to cancer

# Early Chemotherapy

- Targets – rapidly growing cells.

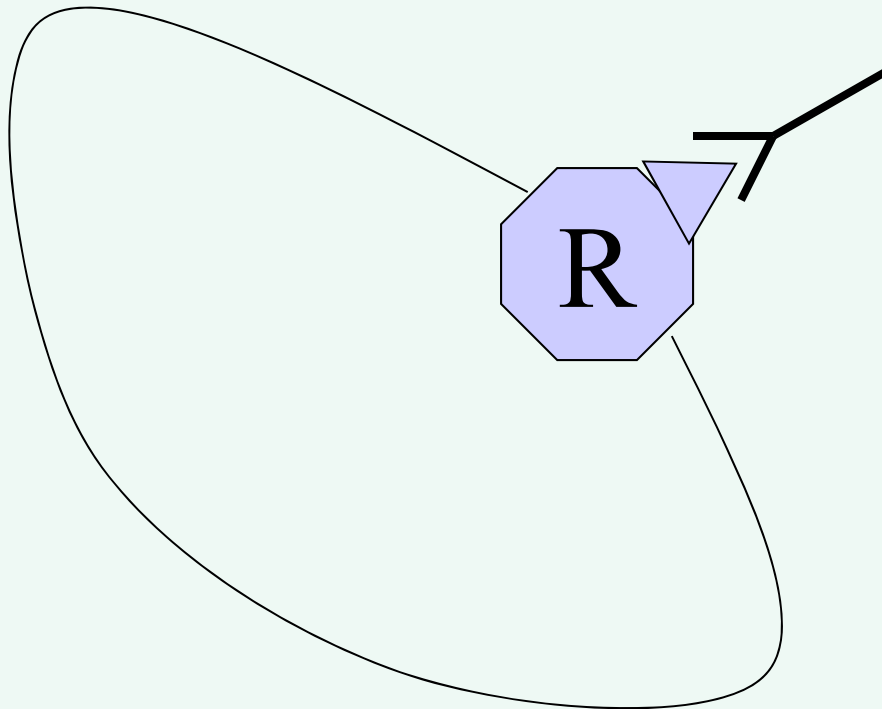
Small molecules ~~to~~ ATP, etc.

NTP ~~to~~ dNTP

dNTPs ~~to~~ DNA

# Drug Antibodies

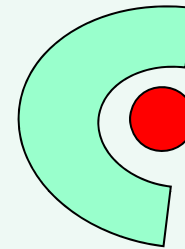
- Antibodies against growth factor receptors or modified forms of the receptors.



- ✓ Antibodies might recruit the immune system
- ✓ Antibodies might block ligand binding to remaining receptors
- ✓ Antibodies might block receptor function

# Small molecule drugs

- Small molecule inhibitors.



- Some of these small molecule drugs are initially effective, but cancer cells can sometimes acquire mutations that make them less effective over time. Some cancer cells make pumps to dump the drugs back out.

# Long term goals

- Ultimately, targeting the stem cells that are cancerous rather than only the most rapidly growing cells will be important.
- Development of specific drugs based on specific cancer situations is also continuing.
- <http://www.cancer.gov/>