Biol 205

Signal Transduction, the Social Contract and Rogue Cancer Cells

Inside cancer web site
http://www.insidecancer.org/
National Cancer Institute
http://www.cancer.gov/cancerinfo/

Reading Assignments:

Chapter 16: Cell Communication

Pgs. 533-543; 545 & Figure 16-15; 557-560; work Q-1, 3, 4, 10, 12, 15, 16, 17, 20 & 23

Chapter 21: Tissues and Cancer

Browse through Cancer section—pgs 726-732. Look at figures 21-47 and 21-52 carefully

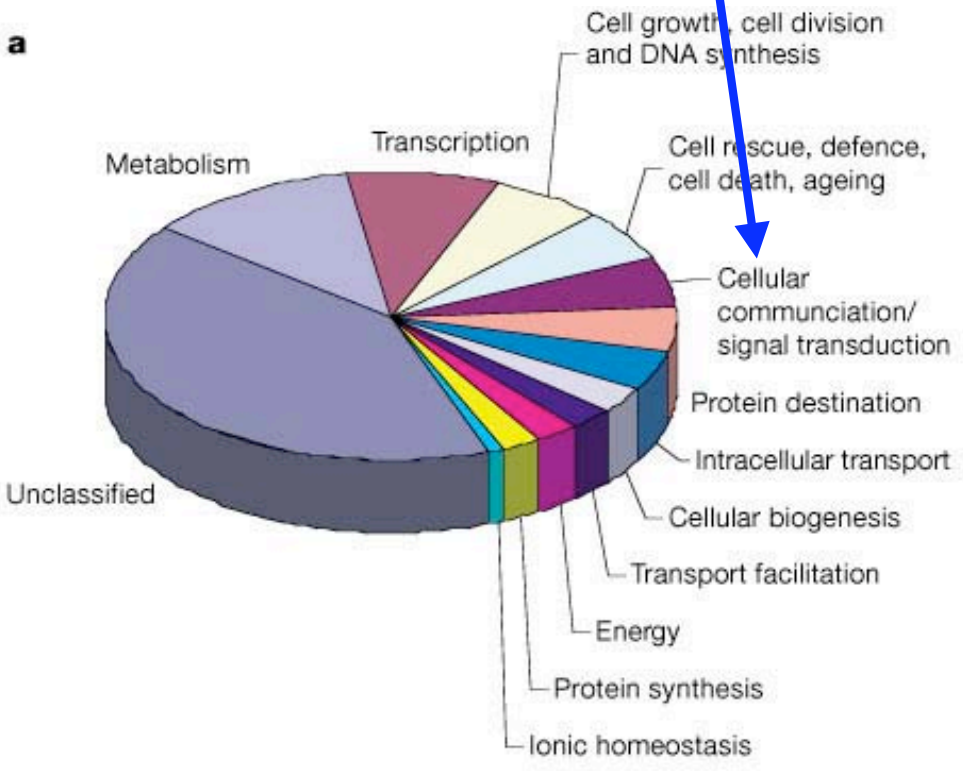
Chapter 4: pg 153-156 on protein phosphorylation. Work Q 4-8

LIGAND: any molecule that binds to a specific site on a protein

Signal Transduction: Everybody does it!

The Arabidopsis thaliana (weedy plant) genome project was recently completed. Here is a breakdown of the functional analysis of the genes discovered in the genome of this organism.

Note that a large proportion of the genes are unclassifed -- meaning no one knows yet what they do for the organism.



Nature 408: 796 Dec. 14, 2000

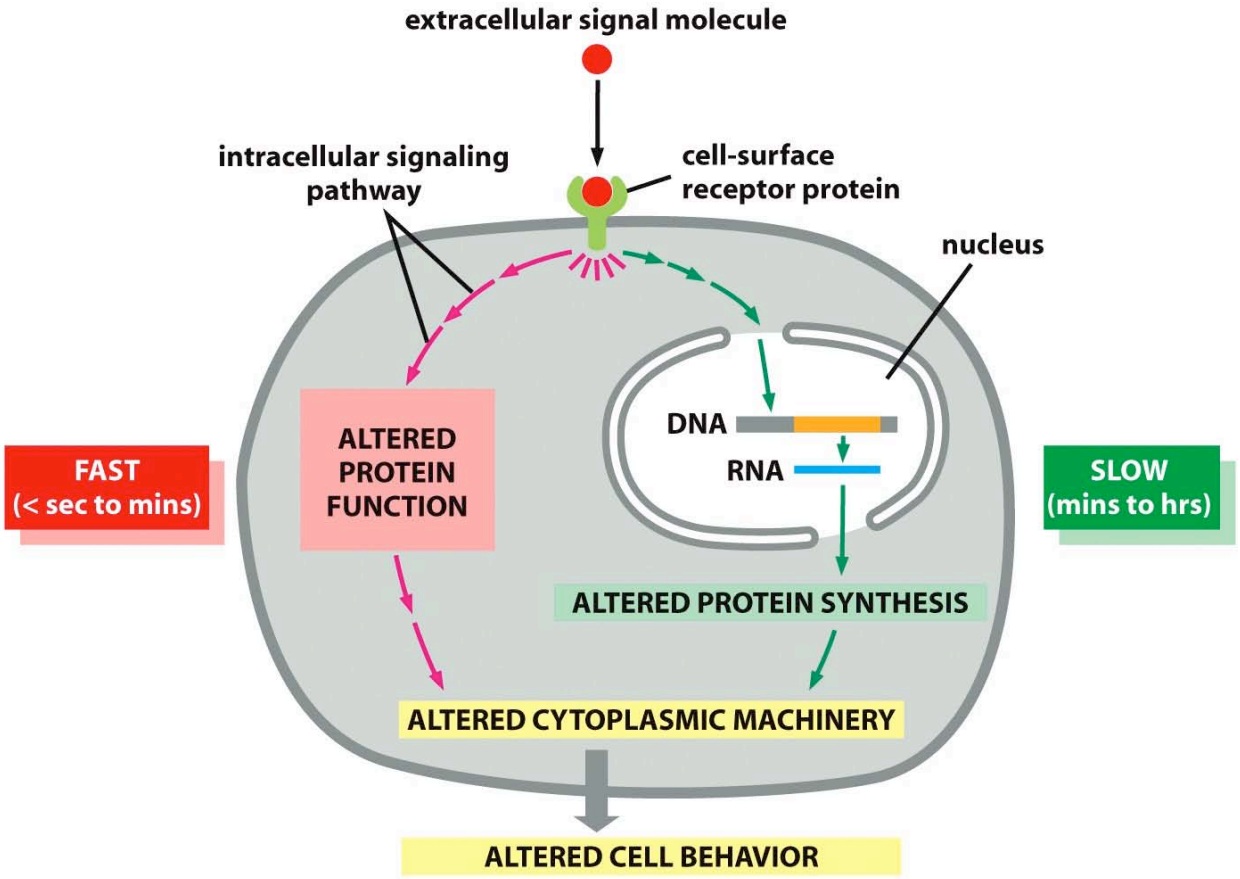
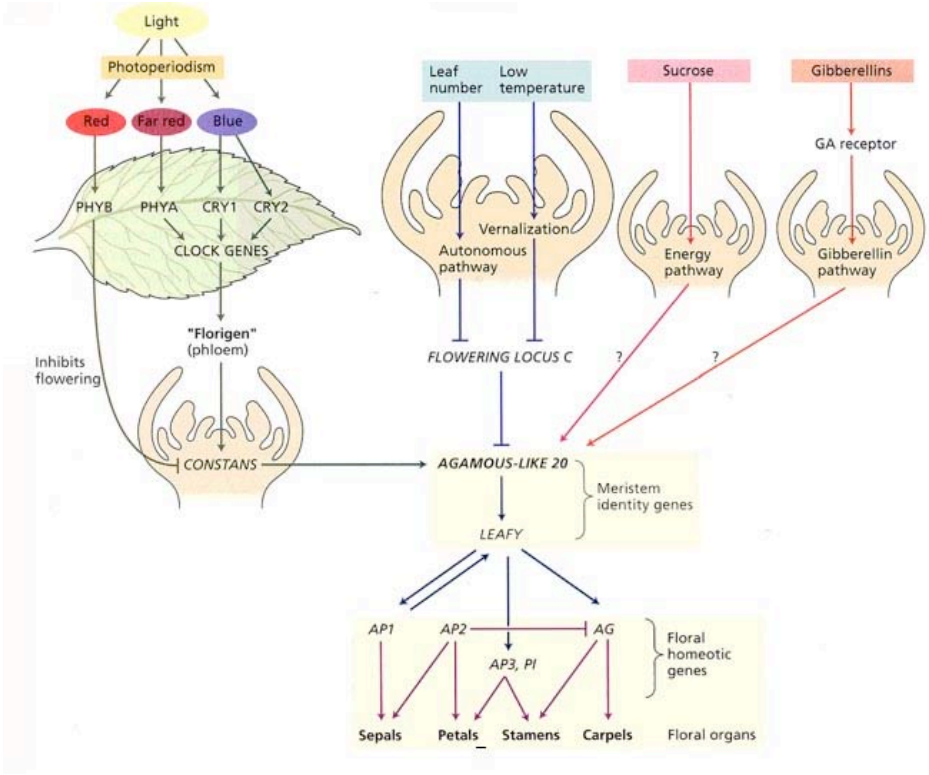


Figure 15-6 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Extracellular signals can act slowly or rapidly to change the behavior of a target cell.

Certain types of signaled responses, such as increased cell growth and division, involve changes in gene expression and the synthesis of new proteins; they therefore occur slowly, often starting after an hour or more. Other responses-such as changes in cell movement, secretion, or metabolism-need not involve changes in gene transcription and therefore occur much more quickly, often starting in seconds or minutes; they may involve the rapid phosphorylation of effector proteins in the cytoplasm, for example. Synaptic responses mediated by changes in membrane potential can occur in milliseconds (not shown).

Environmental signals and developmental events



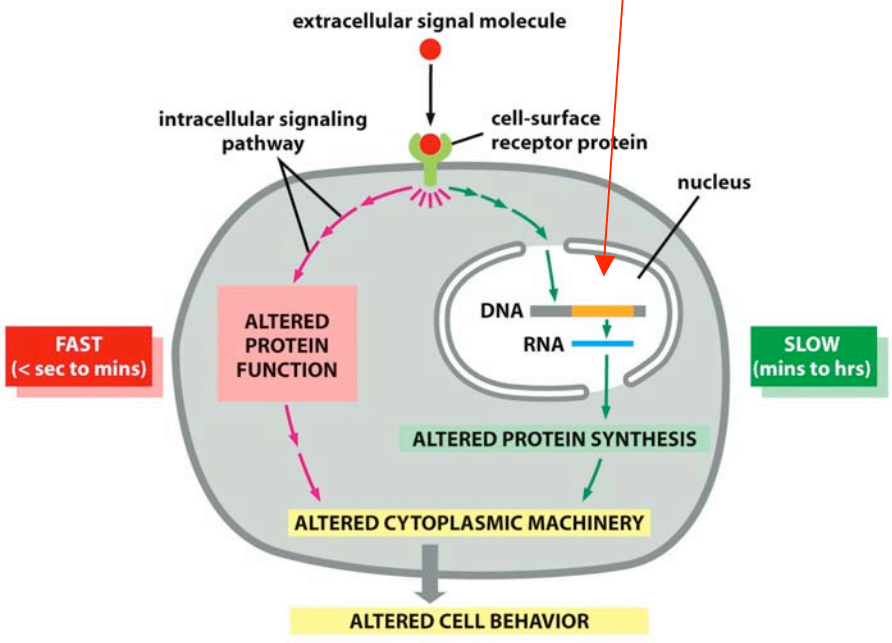


Figure 15-6 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Physiological responses to environmental stressors involves changes in gene expression

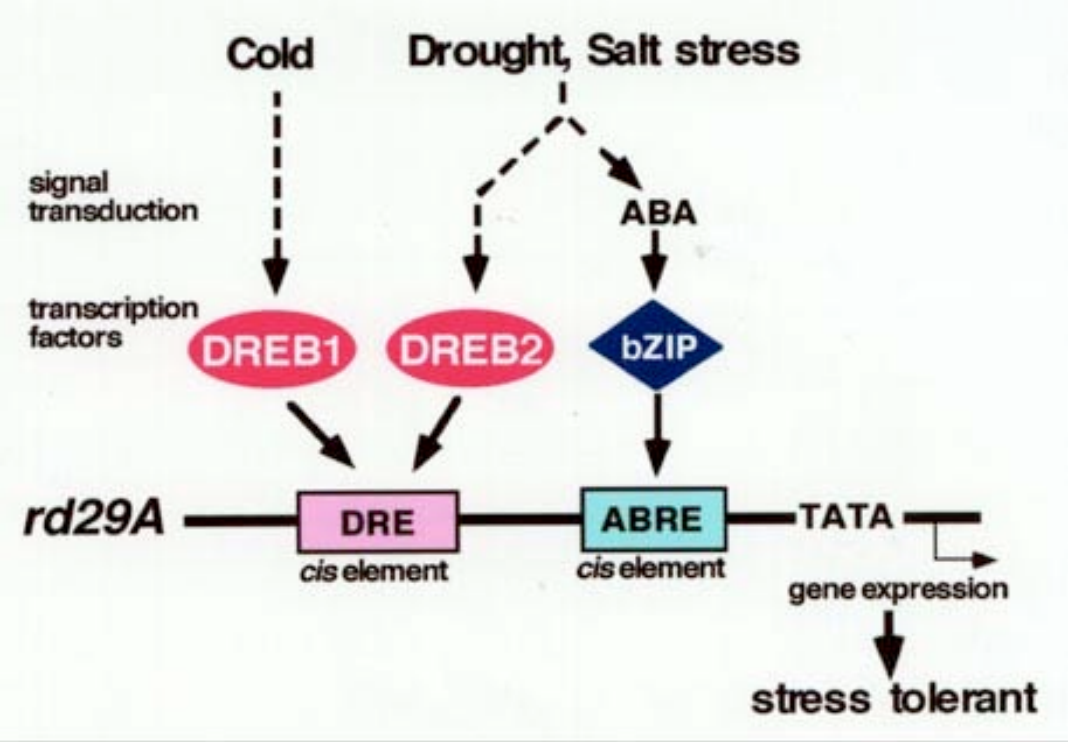


Figure 1. ***A model for the induction of rd29A gene expression under dehydration, high-salt, and low-temperature conditions.*** There are at least two independent signal transduction pathways, ABA-independent and ABA-responsive, between environmental stress and expression of the rd29A gene. DRE functions in the ABA-independent pathway, and ABRE is one of the cis-acting elements in the ABA-responsive induction of rd29A. Two independent DRE binding proteins, DREB1A and DREB2A, function as trans-acting factors and separate two signal transduction pathways in response to cold and drought/high salinity stresses, respectively.

Bacteria can move towards or away from particular chemical (carbon compounds, oxygen, high ionic strength) or physical agents (light)

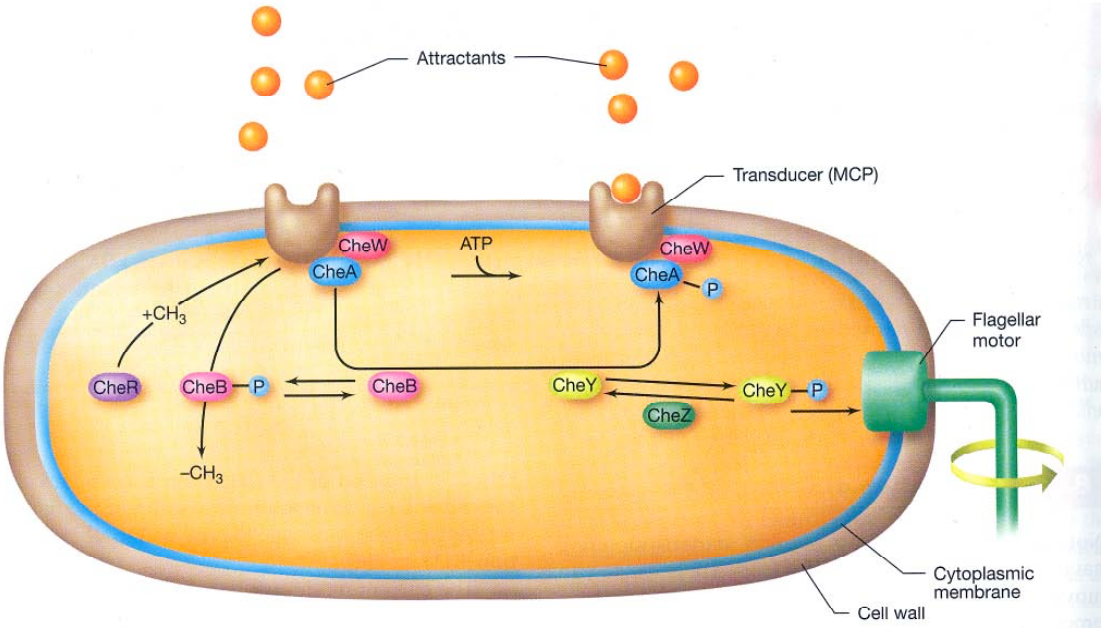


Figure 8.24 Interactions of transducers, chemotaxis (Che) proteins, and the flagellar motor in bacterial chemotaxis. The transducer (MCP forms a complex with the *sensor kinase* CheA and the coupling protein CheW. This combination results in a signal-regulated autophosphory lation of CheA to CheA-P. CheA-P can then phosphorylate the *response regulators* CheB and CheY. Phosphorylated CheY (CheY-P) interacts directly with the flagellar motor switch. CheZ dephosphorylates CheY-P. CheR continually adds methyl groups to the transducer. CheB-P (bu not CheB) removes them. The degree of methylation of the transducers controls their ability to respond to attractants and repellants and leads to adaptation. The structure of the flagellar motor was shown in Figure 4.41.

from BROCK Biology of Microorganisms 10th edition

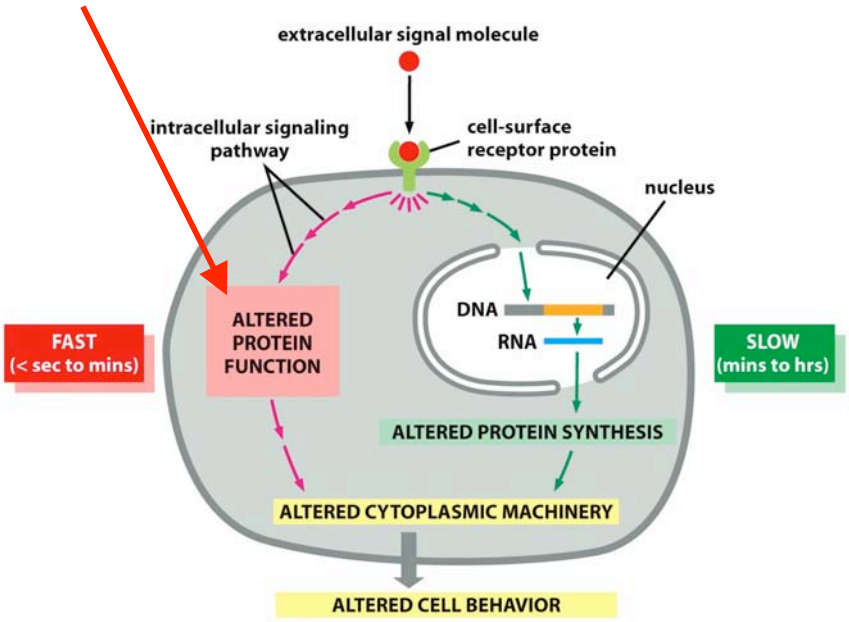


Figure 15-6 Molecular Biology of the Cell 5/e (© Garland Science 2008)

What about signal transduction in animals?

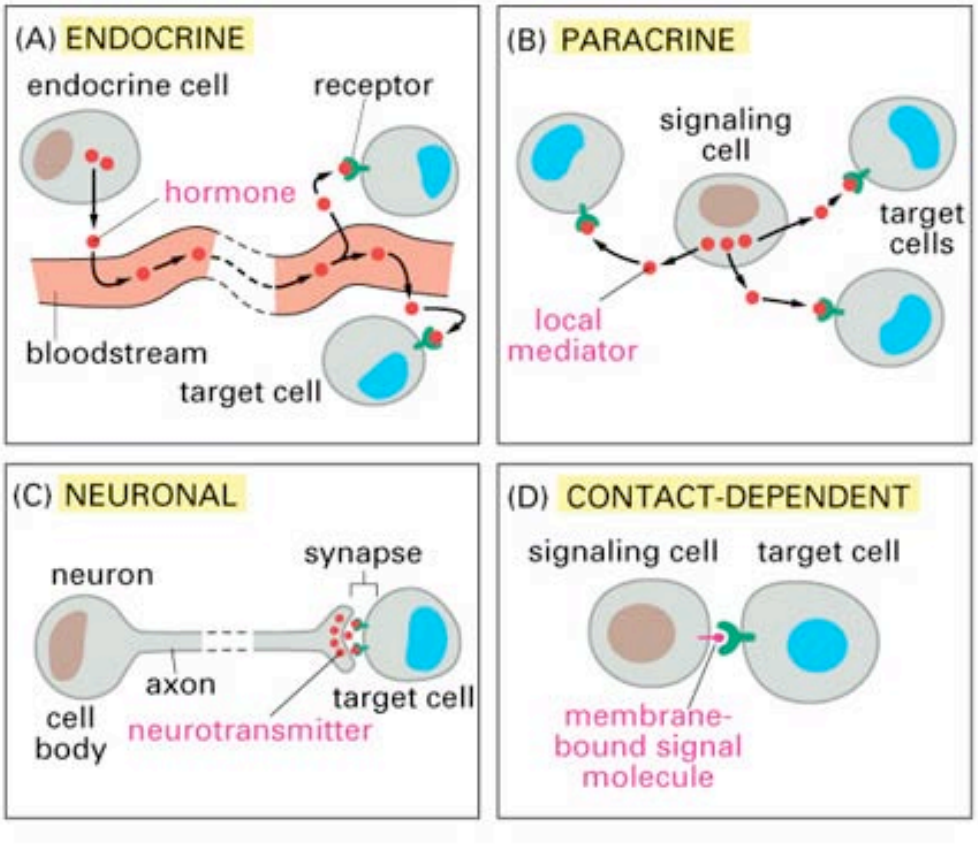


Figure 16-3 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Figure 16–3 Animal cells can signal to one another in various ways.
(A) Hormones produced in endocrine glands are secreted into the bloodstream and are often distributed widely throughout the body. (B) Paracrine signals are released by cells into the extracellular fluid in their neighborhood and act locally. (C) Neuronal signals are transmitted along axons to remote target cells. (D) Cells that maintain an intimate membrane-to-membrane interface can engage in contact-dependent signaling. Many of the same types of signal molecules are used for endocrine, paracrine, and neuronal signaling. The crucial differences lie in the speed and selectivity with which the signals are delivered to their targets.

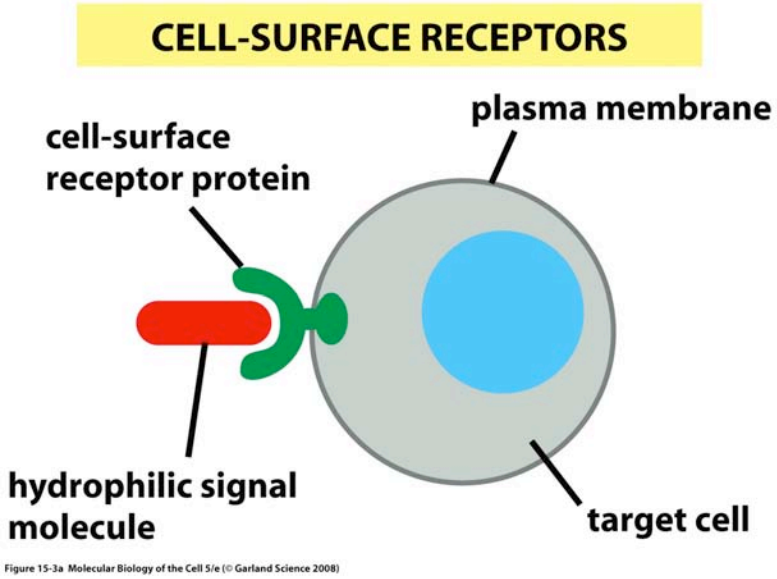


Figure 15-3a Molecular Biology of the Cell 5/e (© Garland Science 2008)

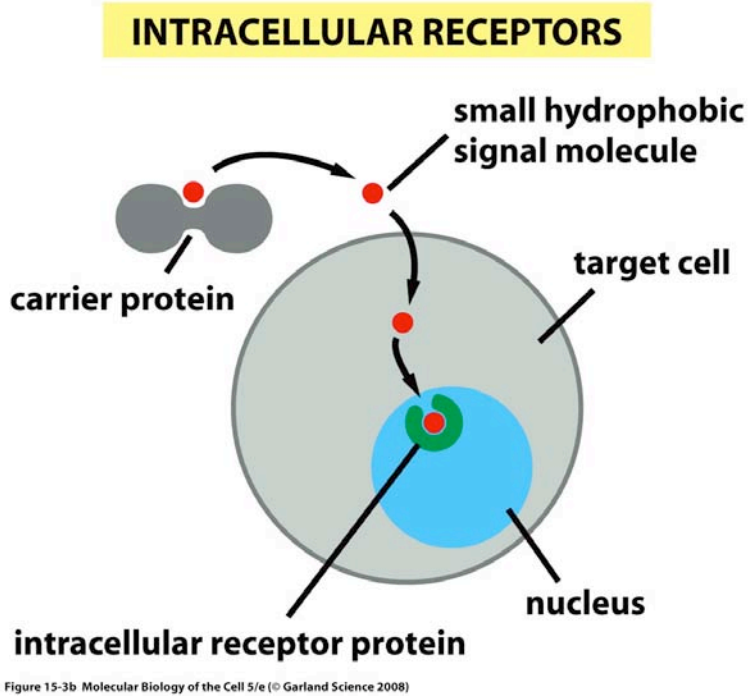


Figure 15-3b Molecular Biology of the Cell 5/e (© Garland Science 2008)

The binding of extracellular signal molecules to either cell-surface or intracellular receptors.

(A) Most signal molecules are hydrophilic and are therefore unable to cross the target cell's plasma membrane directly; instead, they bind to cell-surface receptors, which in turn generate signals inside the target cell (see Figure 15-1). (B) Some small signal molecules, by contrast, diffuse across the plasma membrane and bind to receptor proteins inside the target cell-either in the cytosol or in the nucleus (as shown here). Many of these small signal molecules are hydrophobic and nearly insoluble in aqueous solutions; they are therefore transported in the bloodstream and other extracellular fluids bound to carrier proteins, from which they dissociate before entering the target cell.

Tissue and organ function in multicellular organisms depends absolutely on the ability of cells to properly interact and communicate with each other

Signals from the environment

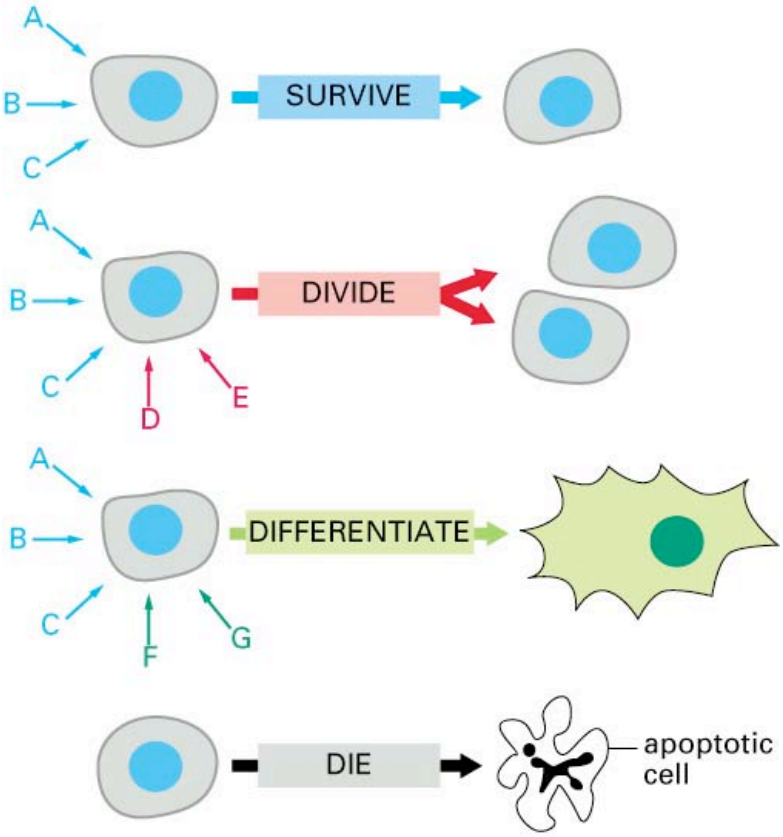


Figure 15–8. Molecular Biology of the Cell, 4th Edition.

An animal cell's dependence on multiple extracellular signals. Each cell types displays a set of receptor proteins tht enables it to respond to a corresponding set of signal molecules produced by other cells. These signal molecules work in combination to regulate the behavior of the cell. As shown here, an indivdual cell requires multiple signals to survive (blue arrows) and additional signals to divide (red arrows) or differentiate (form a specialized cell type -- green arrows). If deprived of appropriate signals, a cell will undergo a form of cell suicide or programmed cell death (apoptosis).

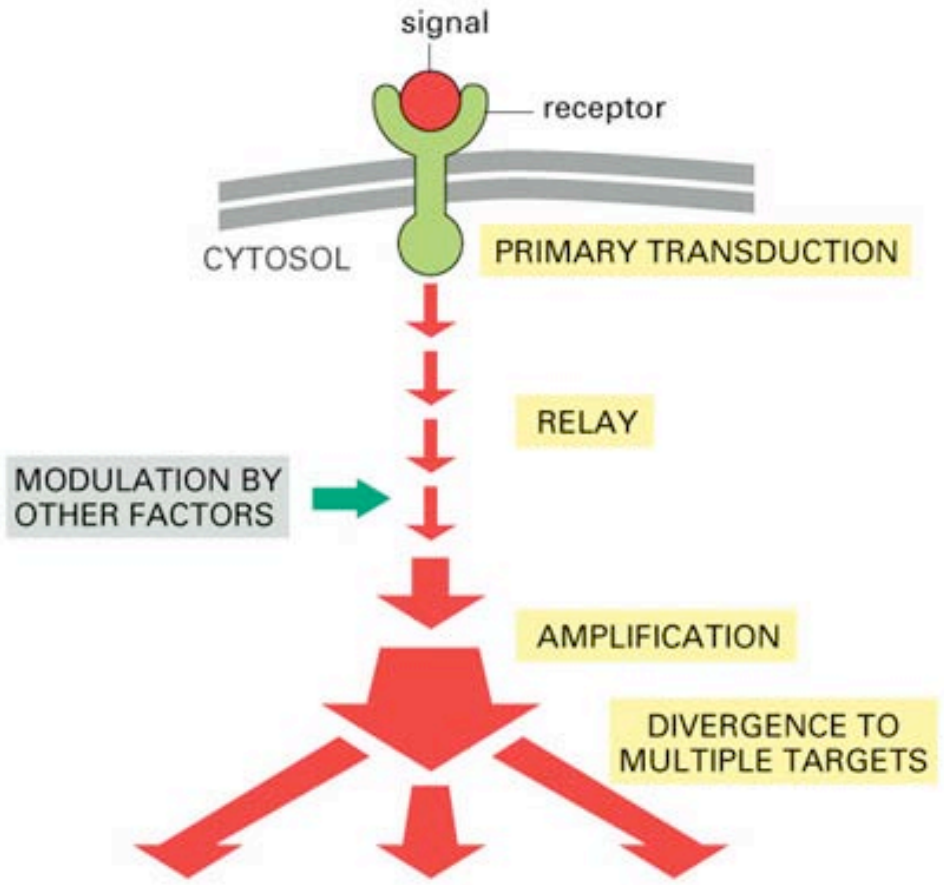


Figure 16-8 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Reception: signalling molecule binds to receptor protein (which may be membrane bound ***or*** intracellular) ONLY cells expressing the receptor protein can respond to the signal

Transduction & Amplification: receptor protein's activity is altered by binding the signalling protein: the signal is "converted" into a form that can bring about a specific cellular response

Response: many possible levels of cellular response

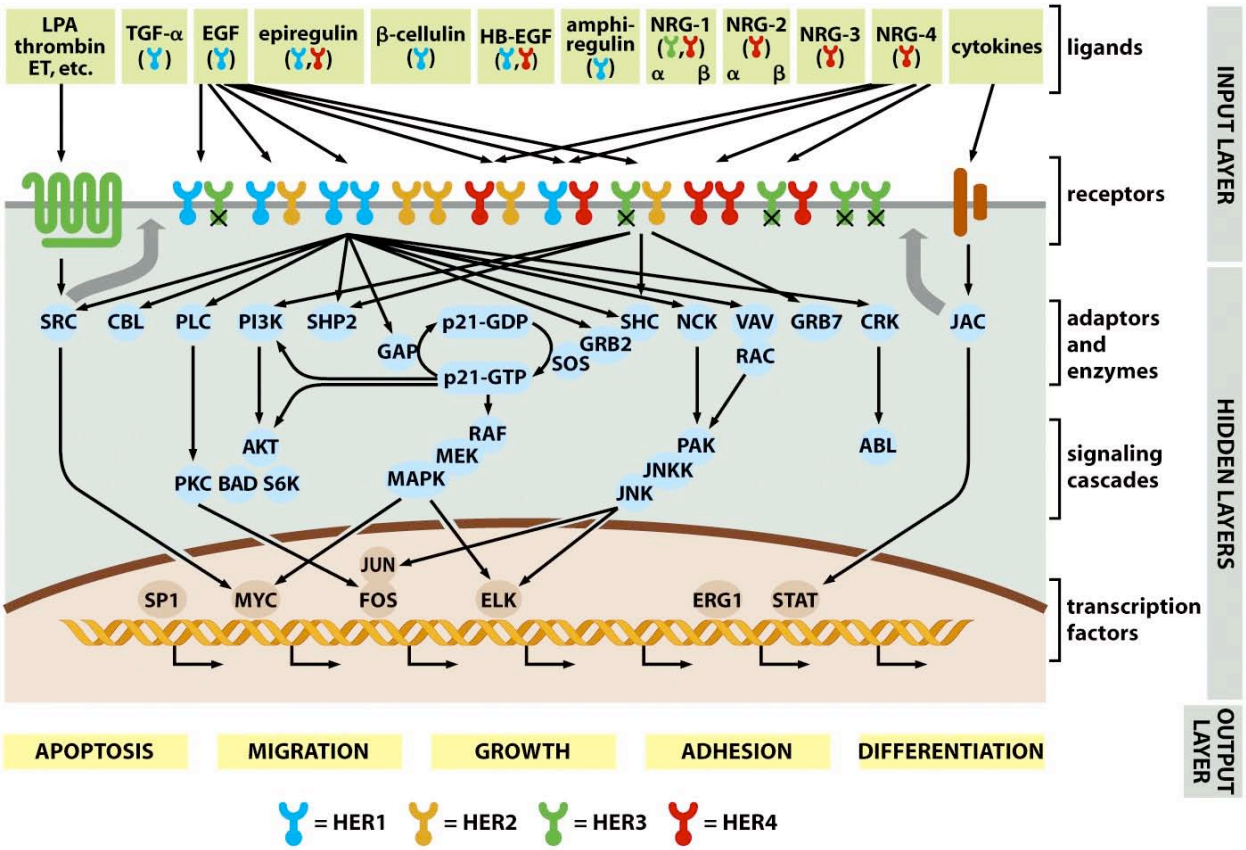
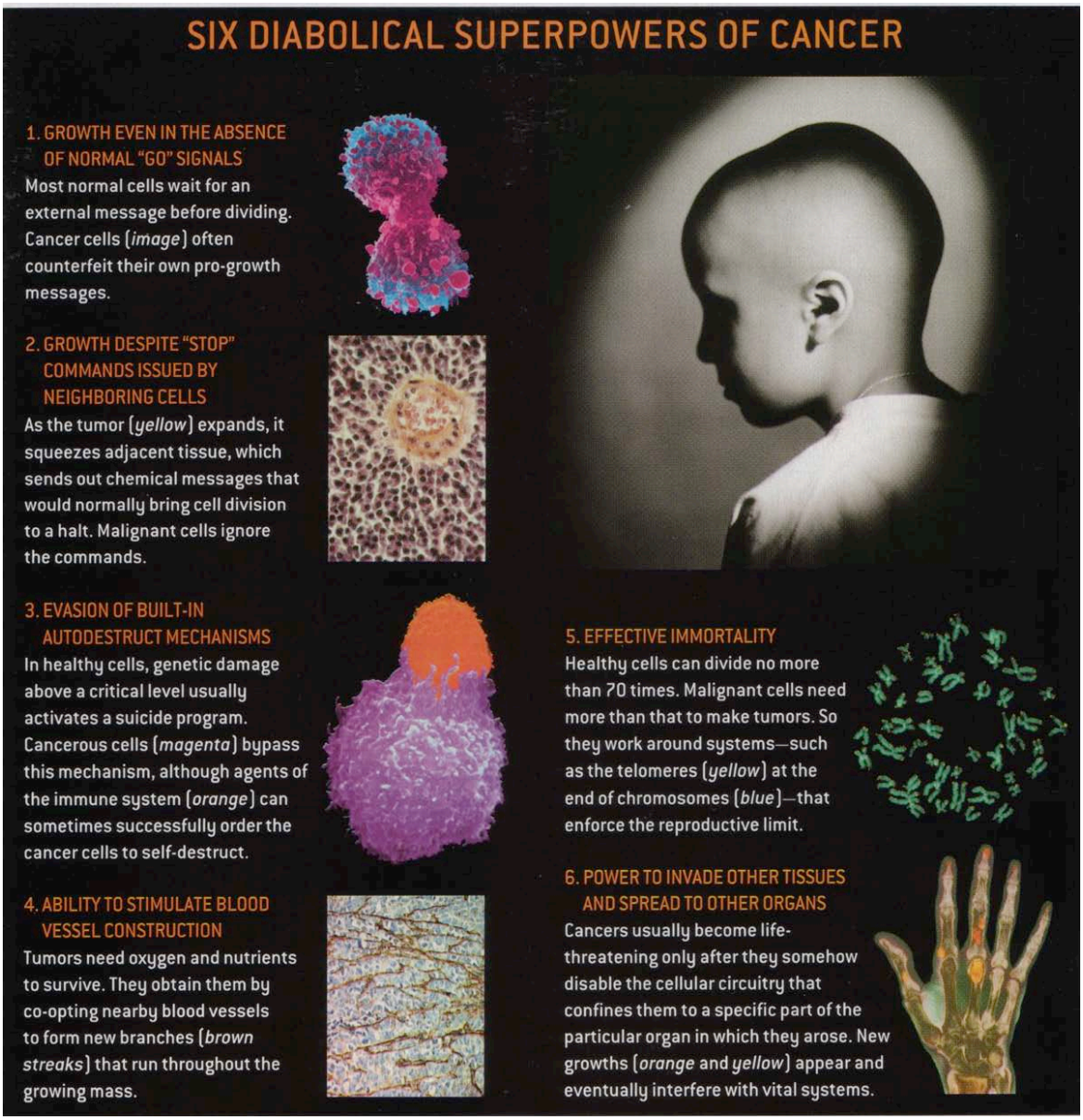


Figure 5-1 The Biology of Cancer (© Garland Science 2007)

How cells communicate with their surroundings

- This cartoon is one representation of how cells communicate with their surroundings. As is indicated here, a variety of protein messengers (ligands, *green squares, top)* interact with a complex array of cell surface receptors, which transduce signals across the plasma membrane *(gray)* into the cytoplasm, where a complex network of signal-transducing proteins processes these signals, funnels signals into the nucleus *(bottom)*, and ultimately evokes a variety of biological responses ("output layer," *yellow rectangles, bottom).*
- **Many of the components of this circuitry, both at the cell surface and in the cell interior, are involved in cancer pathogenesis.**

This cartoon focuses on a small subset of the receptors that are displayed on the surfaces of mammalian cells



Scientific American July 2003

Accessible info on cancer biology and cancer treatment:
http://www.cancer.gov/cancerinfo/

How many somatic cells is an adult human made of?

- An adult human has somewhere around 10^{14} cells
- In the mature organism some cell types divide continually (such as epithelial cells and cell lining the GI tract)
- Other cell types divide rarely
- Since too few or too many cell divisions could produce chaos in a particular organ, the growth and division of each cell type is very carefully controlled
- Cancers result when single cells in the body and change their behavior relative to neighboring cells

- **Early frog embryo cells: 30 minute cycle**
- **Human intestinal epithelia cells: 12 hour cycle**
- **Human liver cells: about 1 year**
- **Other vertebrate cells (such as neurons) exist for months or day or years without growing or dividing**
- **A yeast cell can complete a full cell cycle in 90 min. (Single-celled eukaryotes must also carefully regulate their cell cycle)**

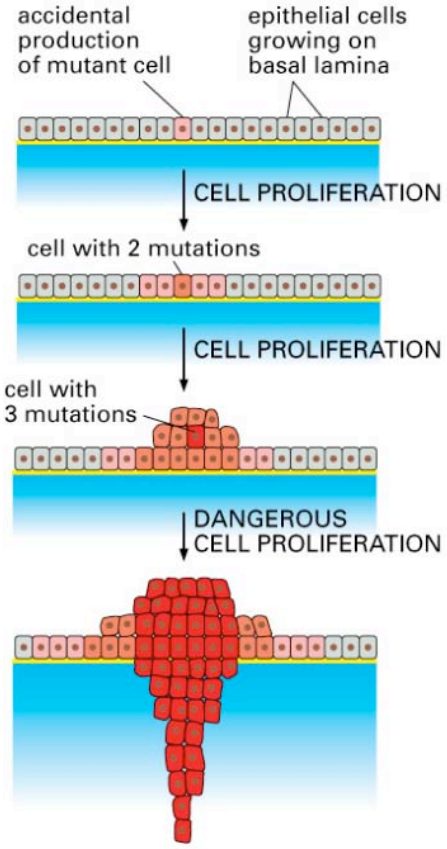
Somatic cells exist in a "social" setting where they need to be responsive to cues from neighboring cells

Cancer cells can be thought of a rogue cells that no longer obey the rules of the social contract

Cancer cells differ from normal cells in the following ways:

1. *The cells mutate so that they can dodge the cellular signals that suppress growth [or that encourage suicide of genetically abnormal cells]*
2. *The cells acquire their own growth-signalling pathways, independent of the external signals that normal metazoan cells are dependent on*
3. They develop limitless potential to proliferate: normal cells can divide only about 70 times before their telomeres (remember?) become so shortened that the chromosomes are damaged and the cell dies
4. Solid tumor cells create their own network of blood vessels *(to supply the growing monster with food and oxygen)*
5. Finally the most dangerous tumor cells are those that can travel to distant sites in the body (metastasis). Nine of ten cancer deaths result from metastases.

Cancers are diseases in which unremitting clonal expansion of somatic cells kills by invading, subverting and eroding normal tissues



A cancer is an aggregate of cells that are clonal descendants of an initial aberrant founder cell

Figure 23–11. Molecular Biology of the Cell, 4th Edition.

- ***A tumor develops through repeated rounds of somatic mutation and proliferation, giving rise eventually to a clone of fully malignant cancer cells.***
- ***Mutations that enhance proliferation increase the chance of that the next step in tumor progression will occur by increasing the size of the cell population at risk of undergoing another mutation.***

Cancer cells reproduce *in defiance of* normal restraints on cell division

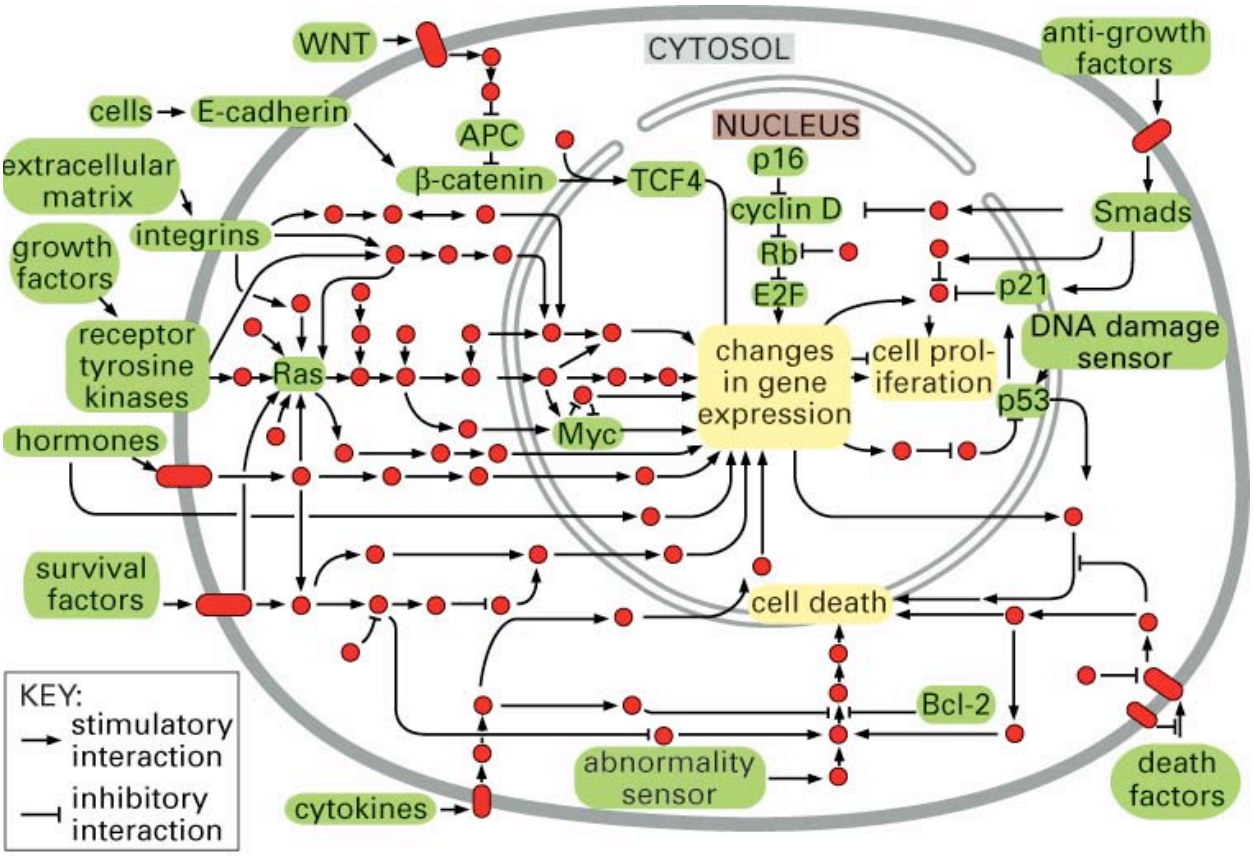
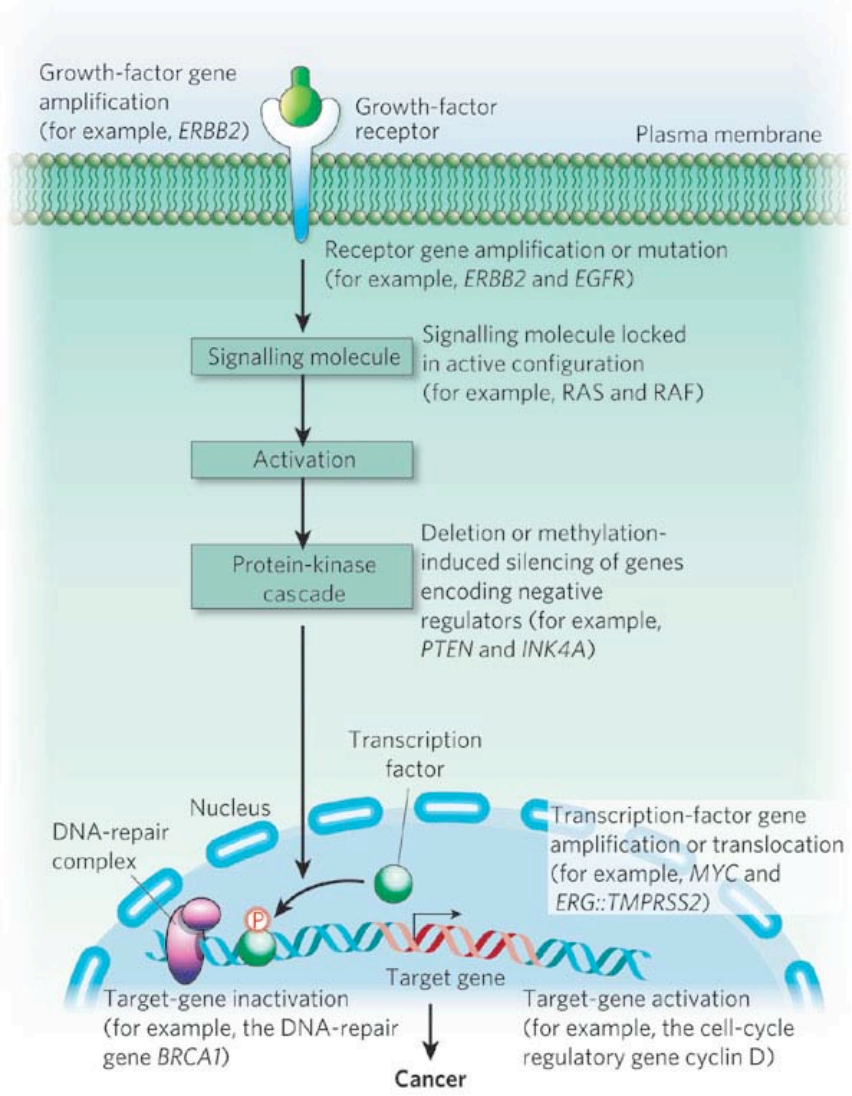


Figure 23–31. Molecular Biology of the Cell, 4th Edition.

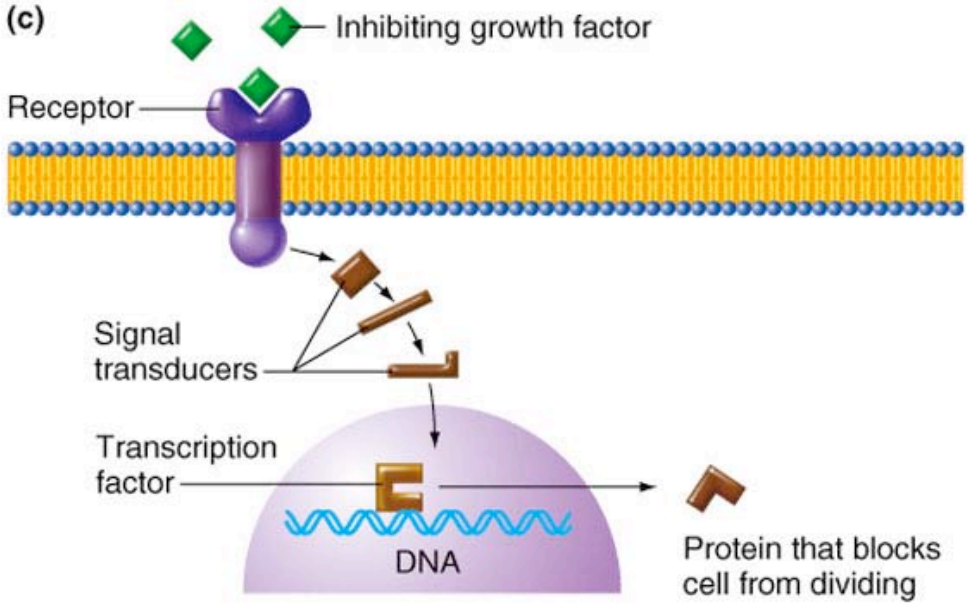
Chart of the major signalling pathways relevant to cancer in human cells, indicating the cellular locations of some of the proteins modified by mutation in cancers.

[Red dots: individual signalling proteins]

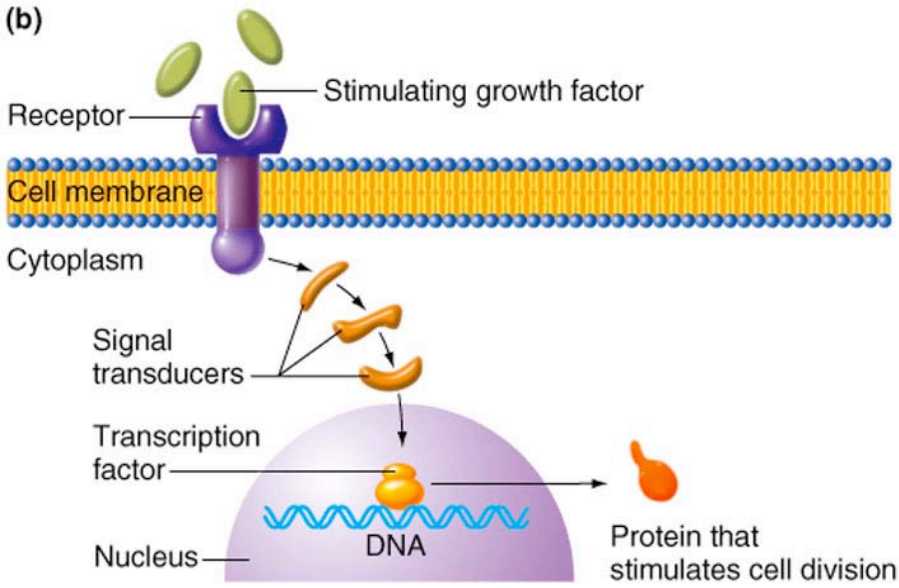


- Most cells "decide" whether or not to divide only after receiving signals from neighboring cells, either positive signals that stimulate division or negative signals that prevent proliferation. ***Many tumor cell, by contrast, make their own stimulatory signals***
- Normal cells dies or commit suicide when starved of growth factors or when heavily damaged by toxins or X-rays or UV light***. Many cancer cells do not exhibit this property.***

Rate of cell proliferation in multicellular organisms is controlled by *growth promoting* and *growth suppressing* signal transduction pathways



What would the effect of loss-of-function mutations in a growth inhibiting pathway be?



What would the effect of loss-of-function mutations in a growth promoting pathway be?

How then can mutations in a growth promoting pathway result in increased cellular proliferation?

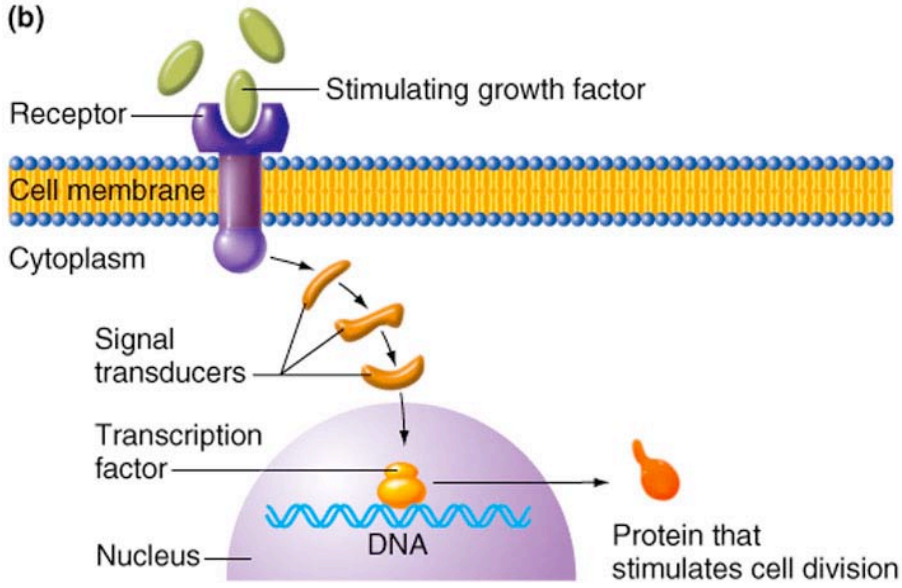
BASIC PRINCIPLE OF SIGNAL TRANSDUCTION:

Normal (wild-type proteins)

NO SIGNAL : NO TRANSDUCTION: NO RESPONSE

SIGNAL : TRANSDUCTION: RESPONSE

Normal Cell: growth(mitosis) stimulating pathway

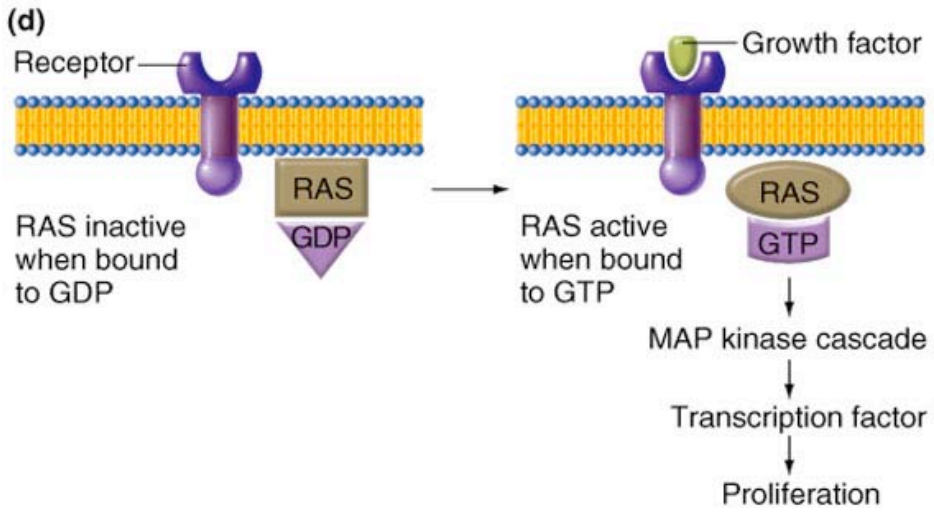


Cancer Cell ("special" gain-of-function mutation in one of the signal transduction components)

NO SIGNAL : TRANSDUCTION: RESPONSE

How is a signal tranduced and transformed? Many possible mechanisms

Look at one example that involves the ras signalling pathway which is mutated in many cancer cells:

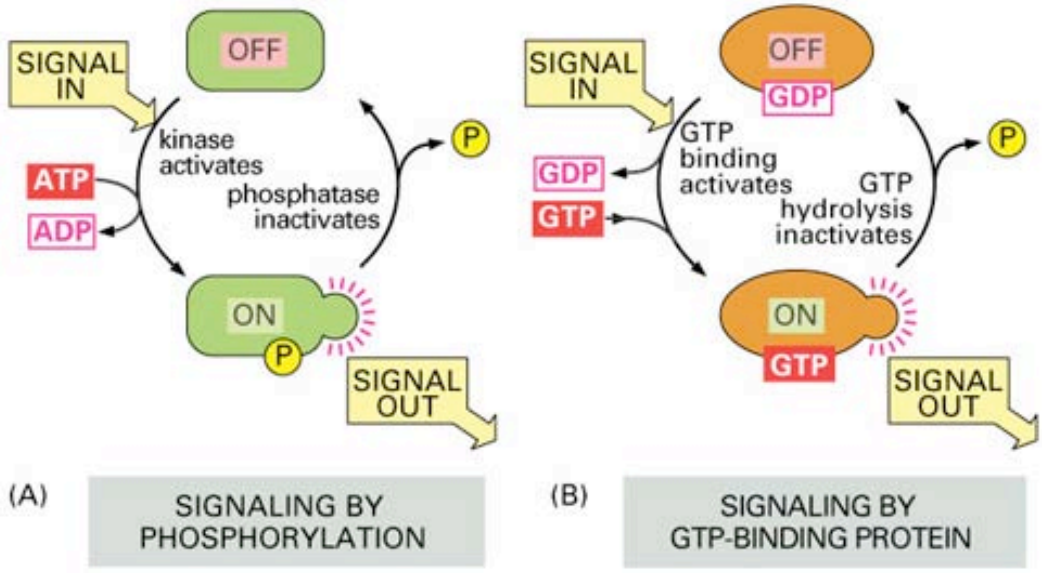


*In the **ras signalling pathway**, the binding of a growth factor to the receptor and the transducion of the signal involves two different mechanisms of post-translational regulation of protein activity – next page*

- *Exchange of a bound GDP for a GTP (Panel B)*
- *Protein phosphorylation: the covalent addition of a phosphate group to a side chain of a protein (such as a tyrosine) by a kinase (Panel A)*

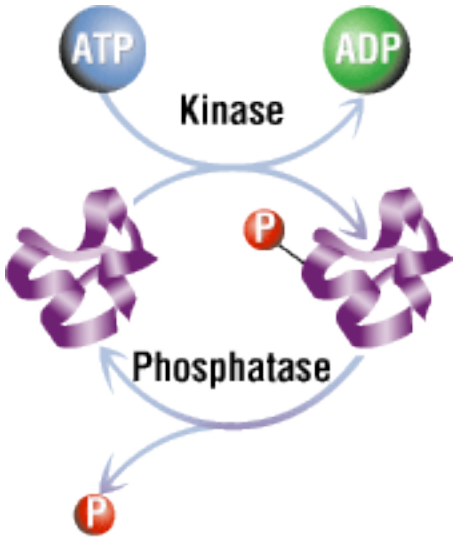
NOTE: inactivation of signal is a critical component of these molecular switches

Add figure 16-15 and pg 545 to your Chapter 16 reading assignment

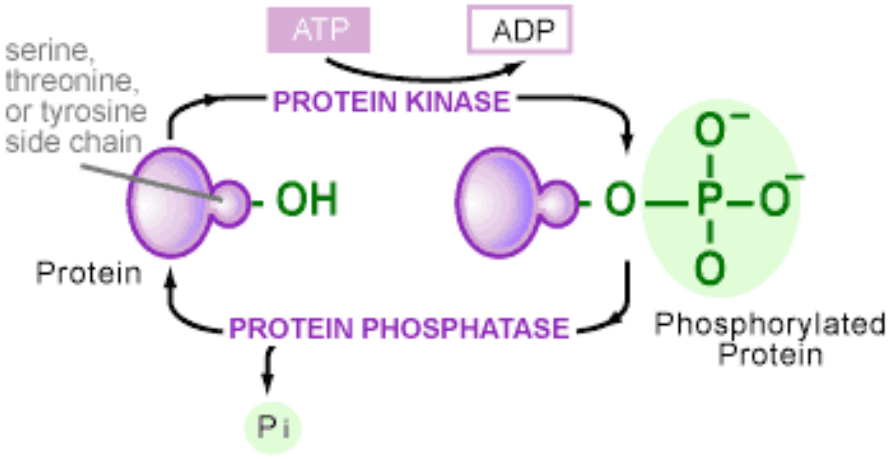


Many Intracellular signaling proteins act as molecular switches.
Intracellular signaling proteins can be activated by the addition of a phosphate group and inactivated by the removal of the phosphate. In some cases, the phosphate is added covalently to the protein by a protein kinase that transfers the terminal phosphate group from ATP to the signaling protein; the phosphate is then removed by a protein phosphatase (A). In other cases, a GTP-binding signaling protein is induced to exchange its bound GDP for GTP, which activates the protein; hydrolysis of the bound GTP to GDP then switches the protein off (B).

Phosphorylation: catalyzed by enzymes called protein ***kinases***
Dephosphorylation: catalyzed by enzymes called *phosphatases*



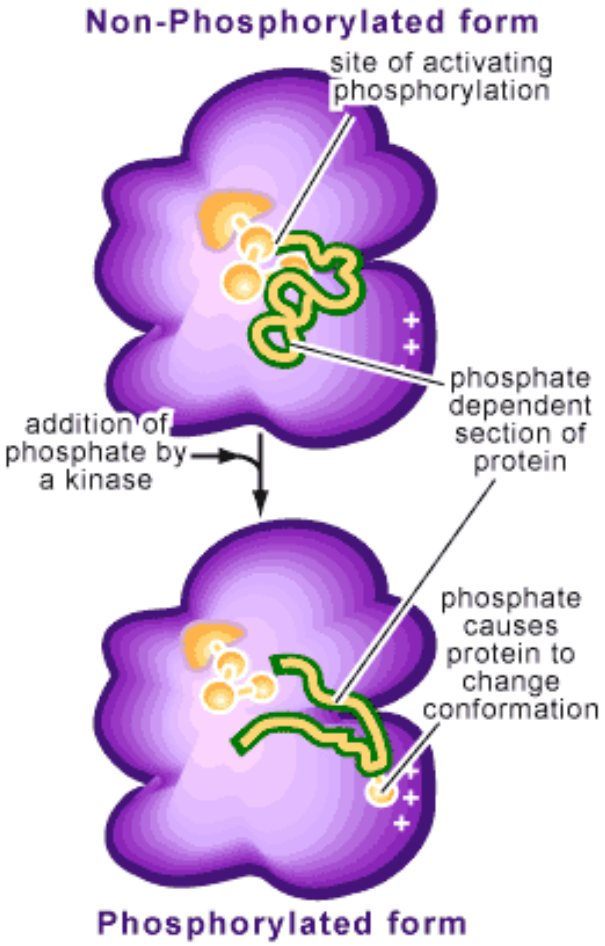
Why would the addition (or subtraction) of a phosphate affect the activity of a protein?

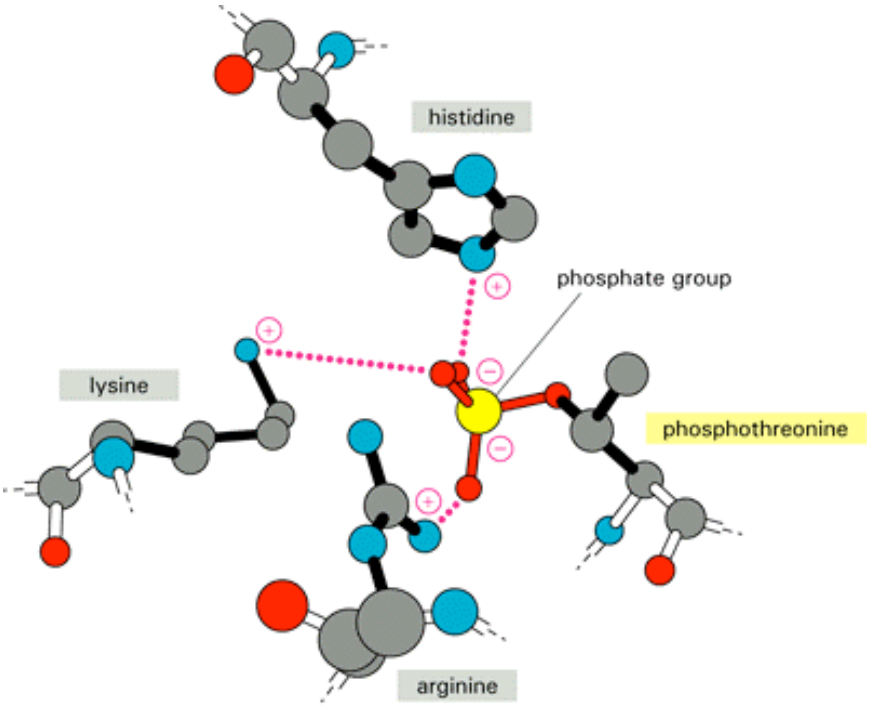


Addition of a phosphate group to a polypeptide will cause a change in the tertiary structure: ***for example, by attracting a cluster of positively charged amino acid side chains (see next page)***

Such a change occuring at one site in the protein can in turn alter the protein's tertiary shape elsewhere

In other words, we are controlling the activity of a protein by changing its shape




histidine
phosphate group
lysine
phosphothreonine
arginine

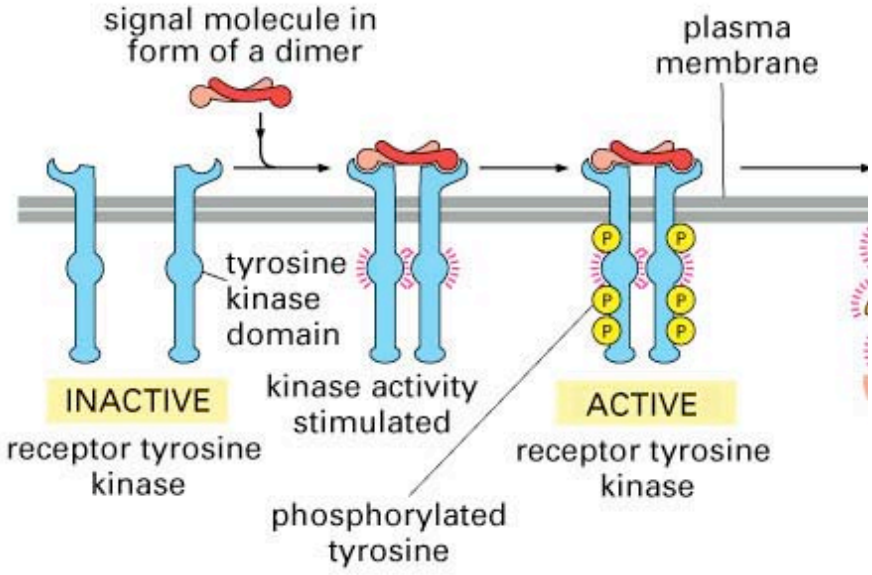
phosphorylation/dephosphorylation of a protein as a control mechanism has many advantages:

- It is rapid, taking as little as a few seconds.
- It does not require new proteins to be made or degraded.
- It is easily reversible.

  - The extensive use of this control mechanism is apparent by the large number of known kinases and phosphatases.
  - Even in a simple organism like yeast, approximately 3 percent of its proteins are kinases or phosphatases.
  - Some of these enzymes are extremely specific, potentially phosphorylating or dephosphorylating only a few target proteins, while others are able to act broadly on many proteins.

Enzyme linked receptor class

(see figure16-14 in text for other types of receptors)

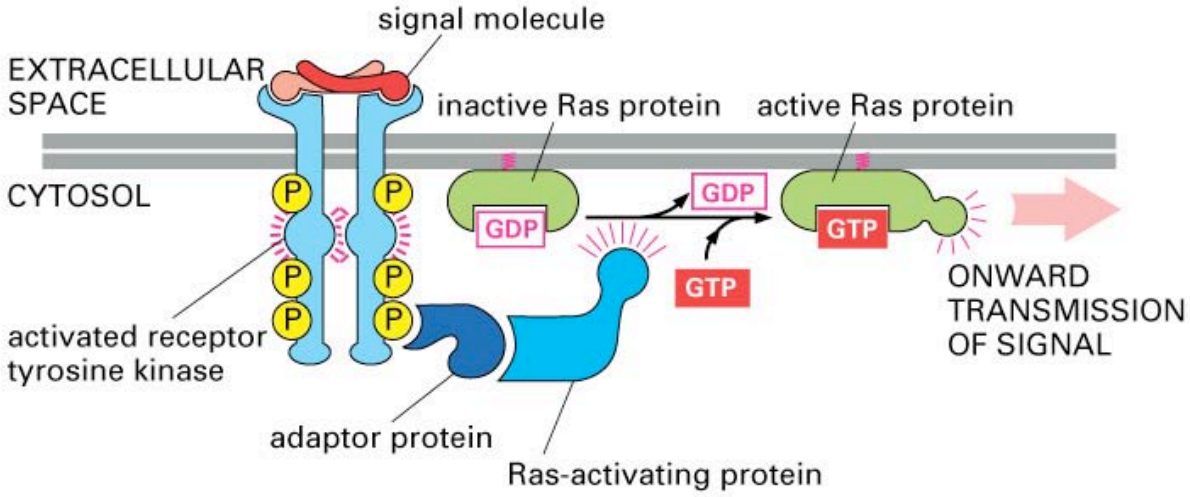


Activation of a receptor tyrosine kinase:

- Binding of signalling molecule causes two receptor molecules to associate into a dimer
- Dimer formation brings the kinase domains of each receptor into close contact and they phosphorylate each other on several tyrosine side chains

NOTE: membrane fluidity is key here

Activated tyrosine kinases transduce the signal to Ras



Virtually all receptor tyrosine kinases activate ***Ras***: a small protein that is bound by a lipid tail to the cytoplasmic face of the plasma membrane

Allosteric control of Ras:

- Inactive when GDP bound
- Active when GTP bound
- After a delay, Ras switches itself off by hydrolyzing GTP to GDP

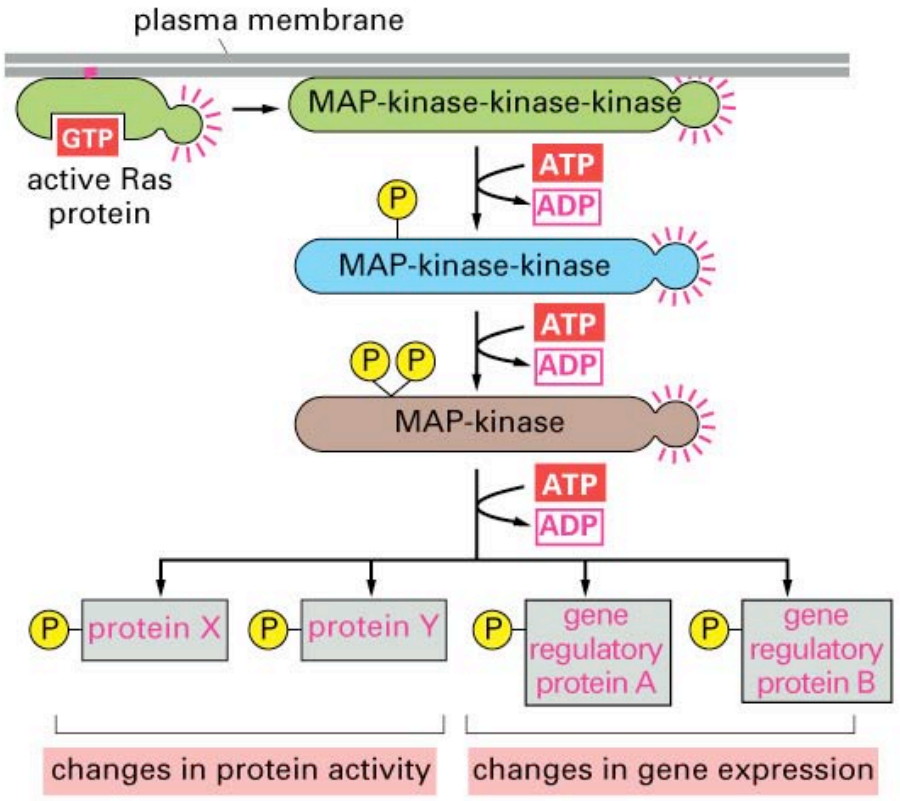


Figure 16-32 Essential Cell Biology, 2/e. (© 2004 Garland Science)

Ras triggers a phosphorylation cascade

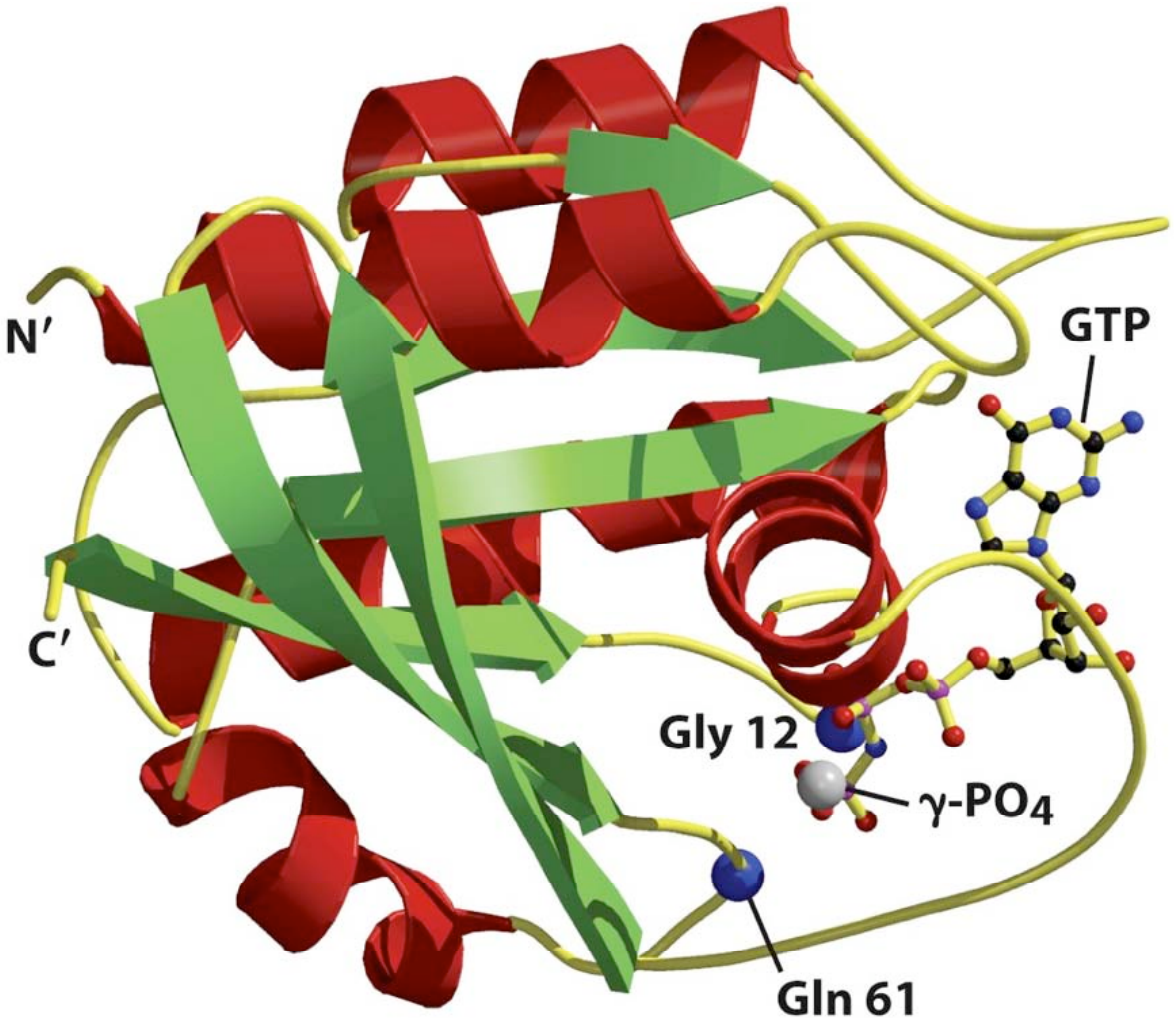
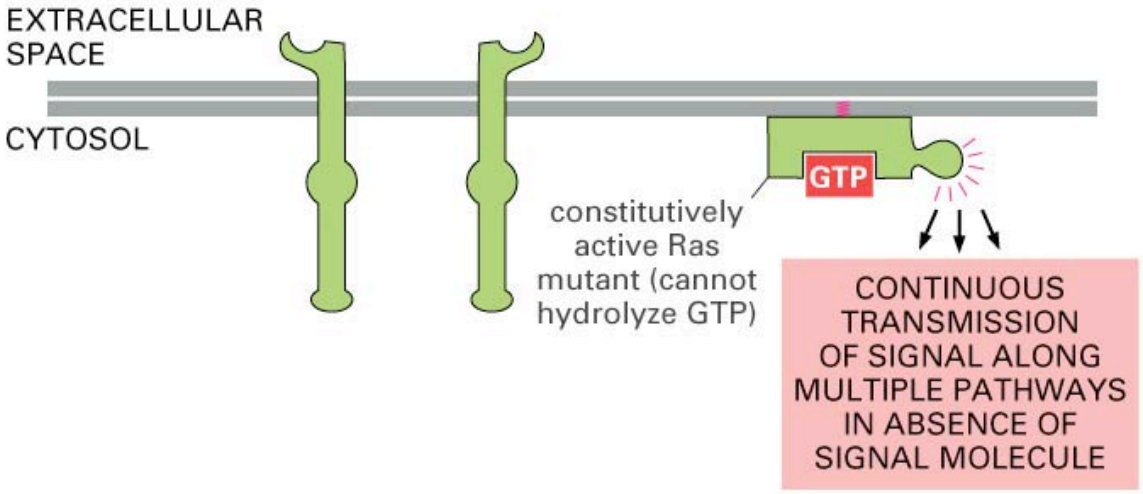


Figure 5-31 The Biology of Cancer (© Garland Science 2007)

Figure 5.31 The structure of the Ras protein
This diagram of the structure of a Ras protein, as determined by X-ray crystallography, depicts the arrangement of the polypeptide backbone of Ras and its α-helical *(red)* and β-pleated sheet *(green)* domains. GTP is indicated as a stick figure, and the two most frequently altered amino acid residues found in human tumor oncoproteins-glycine 12 and glutamine 61-are shown as *blue balls*. As is apparent, both of these residues are closely associated with the γ-phosphate of GTP *(gray ball)*, helping to explain why substitutions of these residues affect the GTPase activity of Ras, and therefore why the codons specifying these residues are preferentially mutated in human tumor cell genomes.

Gain of function mutations in Ras are found in many cancers ~ 40%?



Ras is a type of proto-oncogene (cancer causing when mutated)


SE OF CANCER
f changes before turning
s understand—at the
hat happens, they can
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ns
aviolet light,
t or even the
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es
CELL
STEP 2
... the mistakes add up
It becomes harder and harder for the cells to maintain normal growth, as genes that should be on get turned off and genes that should be off are turned on
1. DNA-REPAIR GENES
These genes make proteins that correct the errors that sometimes occur whenever a cell copies its DNA. If repair genes can't do their job, genetic mistakes start to accumulate
2. TUMOR-SUPPRESSOR GENES
These restrain cell growth and division. Their absence or inactivation takes the brakes off cell multiplication
Signaling enzymes
Tumor suppressors
CELL NUCLEUS
Transcription factors
DNA
Growth-factor protein
Receptor
Signaling enzymes
3. GROWTH GENES
If the genes that regulate normal cell growth and division become stuck in the "on" position, growth continues unabated