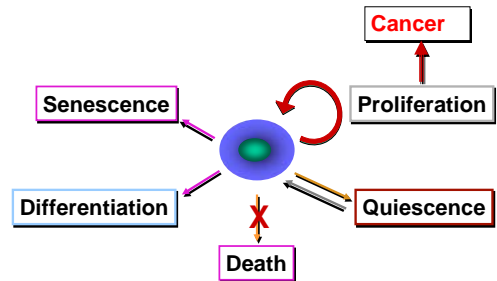


## 细胞信号转导 (Cell Signaling)

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## Fates of a cell



2

## General introduction

Common features of signal transduction  
Cell surface signal transducers, receptors

Ion channels

Secondary messengers

cAMP

cGMP

Lipids

Calcium

G proteins

Trimeric G proteins

Monomeric G proteins, Tyr kinase/MAP kinase

Protein modules

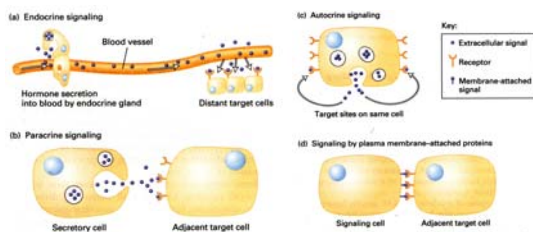
3

## What is "Signal Transduction"?

This expression first made its mark in the biological literature around 1974. Physical scientists and electronic engineers had earlier used the term to describe the conversion of energy or information from one form into another. Signal transduction at the cellular level refers to the movement of signals from outside the cell to inside; cascade of information from the plasma membrane to the nucleus in response to an extracellular stimulus in living organisms.

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## General schemes of intercellular signaling

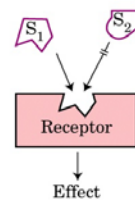


5

## Four basic features of signal-transducing systems

### (a) Specificity

Signal molecule fits binding site on its complementary receptor; other signals do not fit.

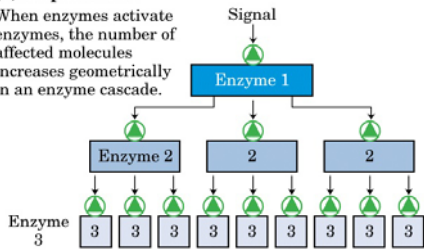


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Four basic features of signal-transducing systems

(b) Amplification

When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.

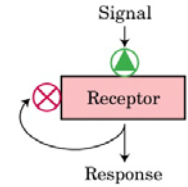


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Four basic features of signal-transducing systems

(c) Desensitization/Adaptation

Receptor activation triggers a feedback circuit that shuts off the receptor or removes it from the cell surface.

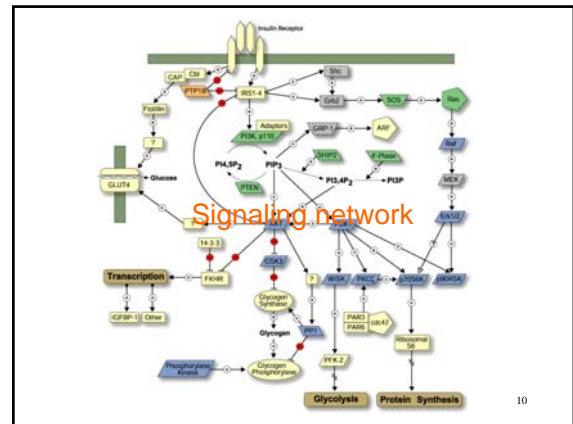
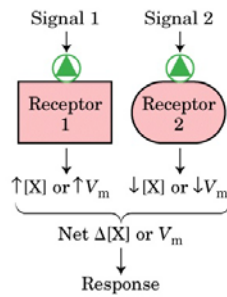


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Four basic features of signal-transducing systems

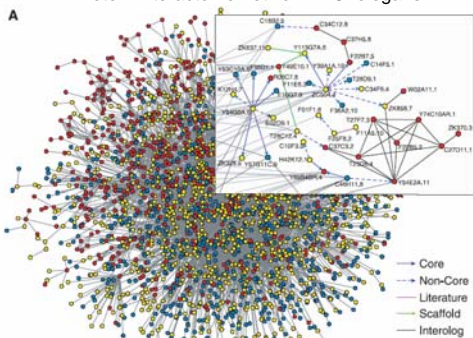
(d) Integration

When two signals have opposite effects on a metabolic characteristic such as the concentration of a second messenger X, or the membrane potential  $V_m$ , the regulatory outcome results from the integrated input from both receptors.



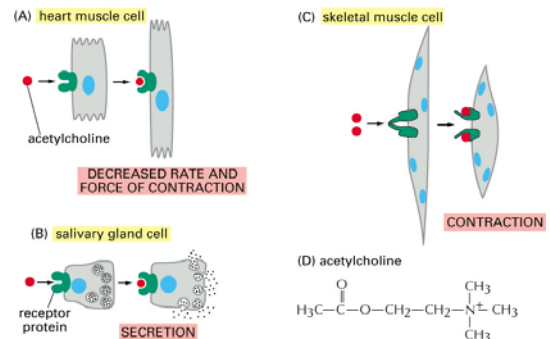
10

Protein interactome network in *C. elegans*

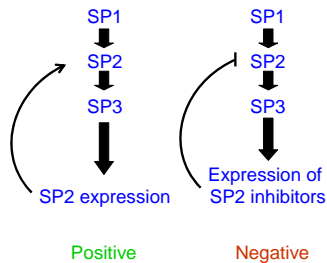


Li, et al., 2004, Science, 303:540

Context-specificity of cell signaling: Different cells respond differently to the same extracellular signal

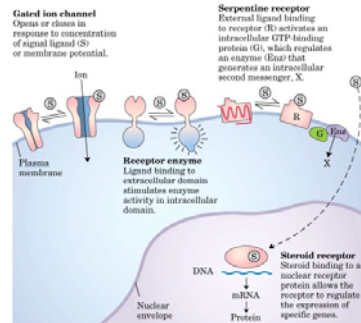


### Positive and negative feedback mechanisms



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### Four general types of signal transducers



14

### Ligand-activated cell-surface receptors

- Ion-channel receptors: acetylcholine
- G-protein-coupled receptors: epinephrine, glucagon, serotonin
- Tyrosine kinase-linked receptors: interferons
- Tyrosine kinase receptors: EGF, PDGF, insulin
- Tyrosine phosphatase receptors: CD45
- Serine/threonine kinase receptors: TGF $\beta$ , BMP
- Guanylate cyclase receptor: atrial natriuretic factor

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### General introduction

- Common features of signal transduction
- Cell surface signal transducers, receptors

### Ion channels

### Secondary messengers

- cAMP
- cGMP
- Lipids
- Calcium

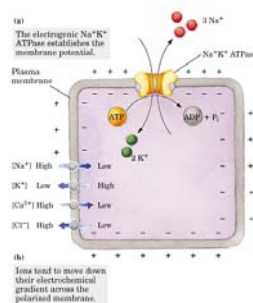
### G proteins

- Trimeric G proteins
- Monomeric G proteins, Tyr kinase/MAP kinase

### Protein modules

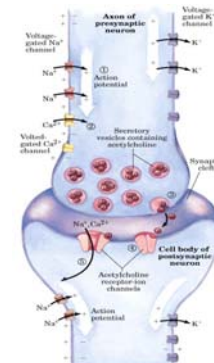
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### Transmembrane electrical potential



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### Role of voltage-gated and ligand-gated ion channels in neural transmission



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General introduction  
 Common features of signal transduction  
 Cell surface signal transducers, receptors  
 Ion channels  
 Secondary messengers  
 cAMP  
 cGMP  
 Lipids  
 Calcium  
 G proteins  
 Trimeric G proteins  
 Monomeric G proteins, Tyr kinase/MAP kinase  
 Protein modules

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## Second messengers

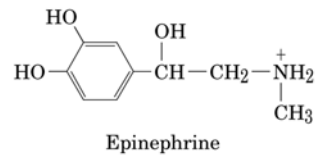


20

Secondary messengers:

cAMP  
 cGMP  
 Lipids  
 Calcium

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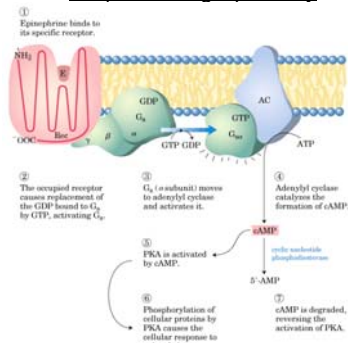


Epinephrine

Produced by Chromaffin cells in adrenal medulla  
 Functions:  
 Increase heart rate, blood pressure,  
 sweating, rate of respiration  
 Stimulate conversion of glycogen to glucose

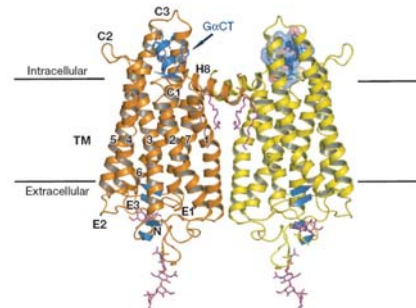
22

## Transduction of the epinephrine signal: the $\beta$ -adrenergic pathway



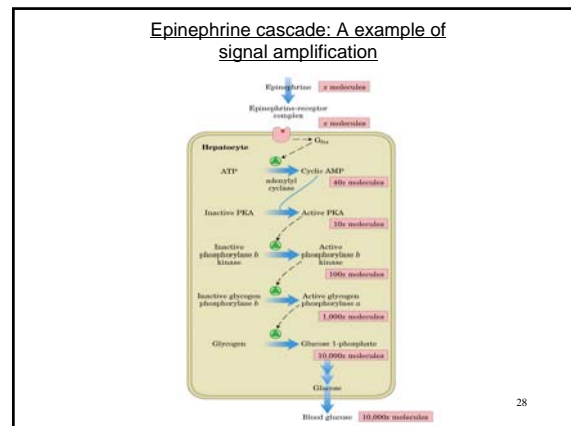
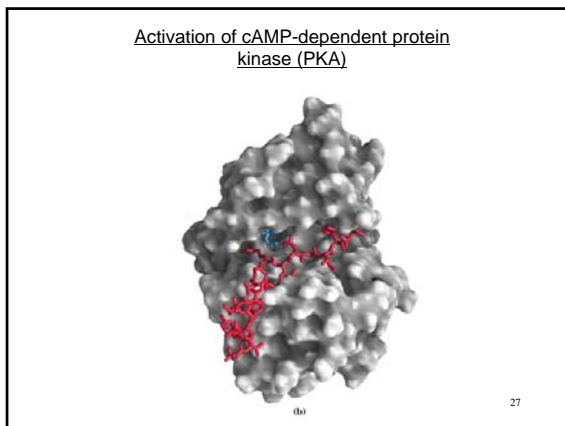
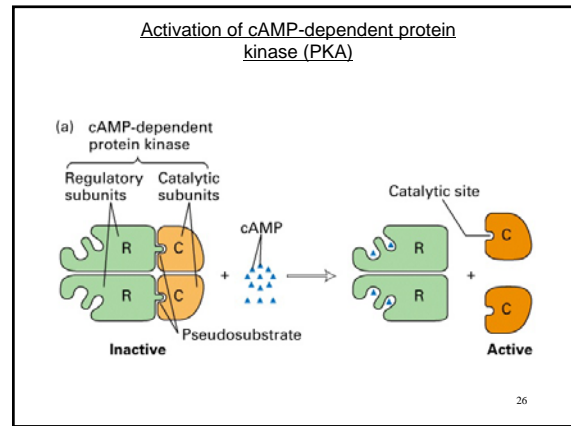
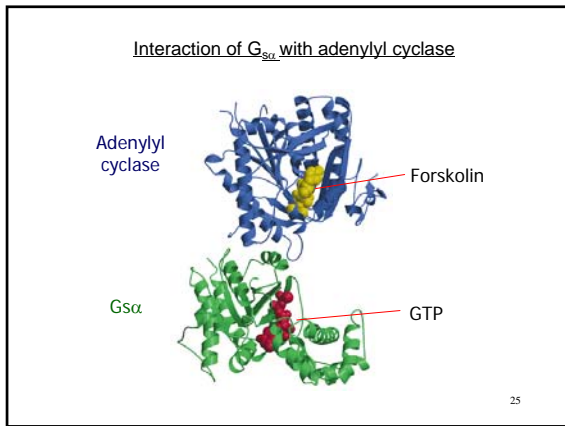
23

## Structure of Opsin associated with the C-terminal Gs $\alpha$



Scheerer et al. Nature, 2008

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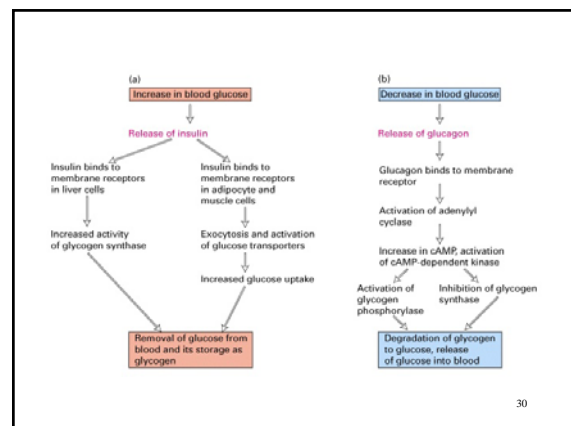
### cAMP as a secondary messenger

**TABLE 20-3** Metabolic Responses to Hormone-Induced Rise in cAMP in Various Tissues

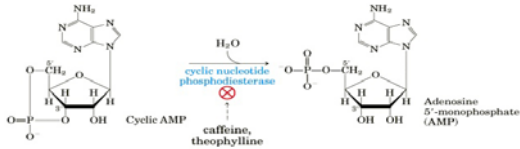
Tissue	Hormone Inducing Rise in cAMP	Metabolic Response
Adipose	Epinephrine; ACTH; glucagon	Increase in hydrolysis of triglyceride; decrease in amino acid uptake
Liver	Epinephrine; norepinephrine; glucagon	Increase in conversion of glycogen to glucose; inhibition of synthesis of glycogen; increase in amino acid uptake; increase in gluconeogenesis (synthesis of glucose from amino acids)
Ovarian follicle	FSH; LH	Increase in synthesis of estrogen, progesterone
Adrenal cortex	ACTH	Increase in synthesis of aldosterone, cortisol
Cardiac muscle cells	Epinephrine	Increase in contraction rate
Thyroid	TSH	Secretion of thyroxine
Bone cells	Parathyroid hormone	Increase in resorption of calcium from bone
Skeletal muscle	Epinephrine	Conversion of glycogen to glucose
Intestine	Epinephrine	Fluid secretion
Kidney	Vasopressin	Resorption of water
Blood platelets	Prostaglandin I	Inhibition of aggregation and secretion

SOURCE: E. W. Sutherland, 1972, *Science* 177:401.

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### Inactivation of cAMP



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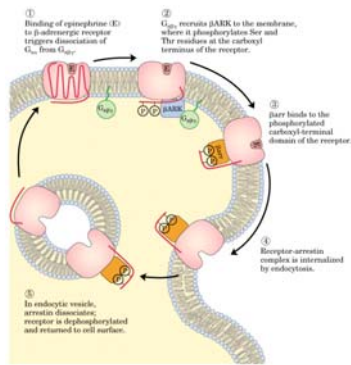
### Medicine: $\beta$ -adrenergic receptor

Cardiac muscle cells possess  $\beta_1$  receptor, whose activation increases heart rate. Practolol (心得灵), an  $\beta_1$ -selective antagonist, can slow heart contraction and is used to treat cardiac arrhythmia and angina.

Smooth muscle cells have  $\beta_2$  receptors, whose activation promotes relaxation. Terbutaline (特布他林), an agonist selective for  $\beta_2$ , is used in the treatment of asthma.

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### Desensitization of the $\beta$ -adrenergic receptor



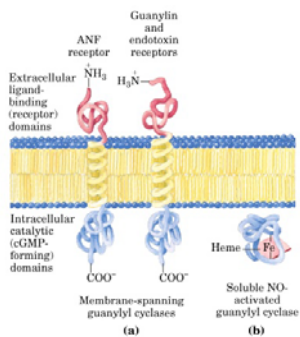
33

### Secondary messengers:

- cAMP
- cGMP
- Lipids
- Calcium

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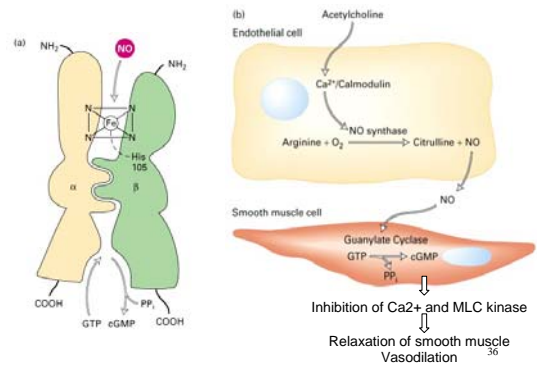
### Guanylyl cyclases



Endotoxin, produced by *E. coli* and other gram-negative bacteria in intestine, stimulates cGMP production, increases Cl<sup>-</sup> secretion and consequently decreases reabsorption of water by the intestinal epithelium, producing diarrhea

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### NO (Nitric Oxide) signaling



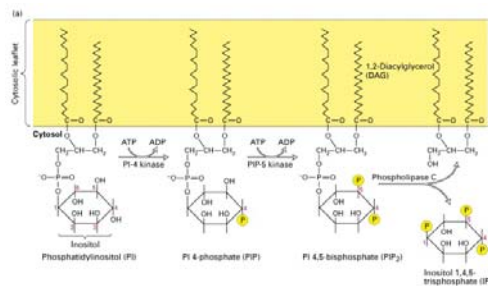
36

Secondary messengers:

- cAMP
- cGMP
- Lipids
- Calcium

37

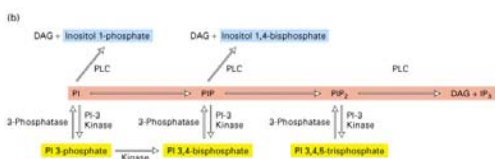
### Lipids as messengers



磷脂酰肌醇

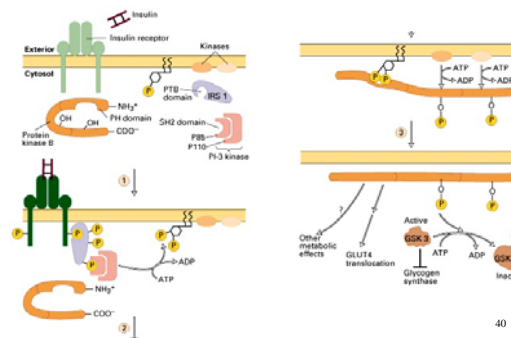
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### Lipid phosphorylation



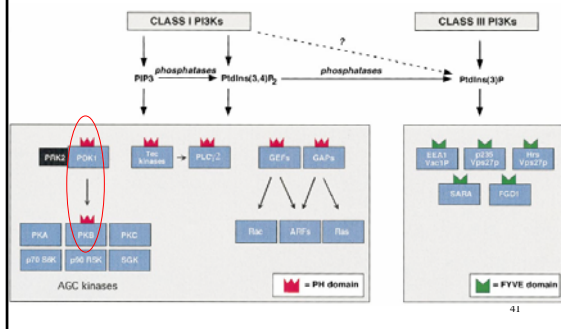
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### Insulin regulates glucose metabolism via PI3K



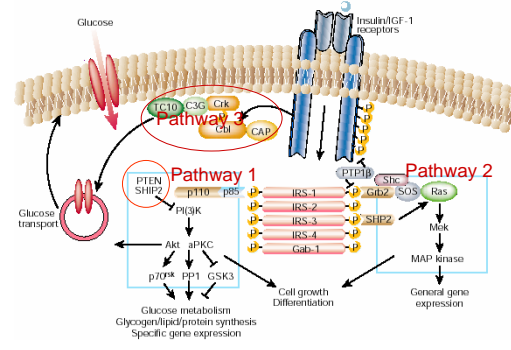
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### PH domain-containing proteins

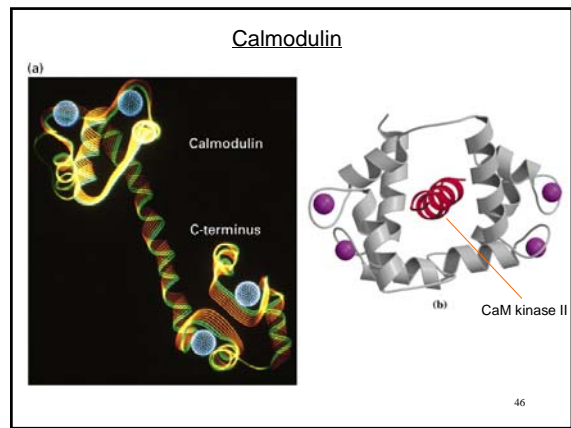
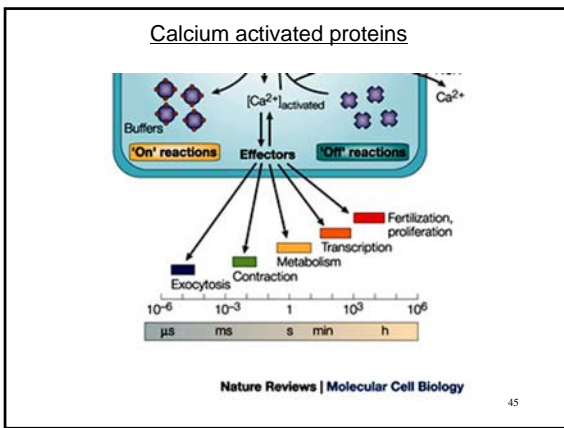
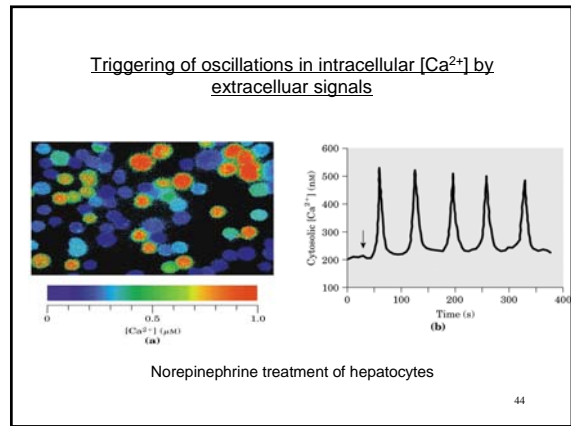
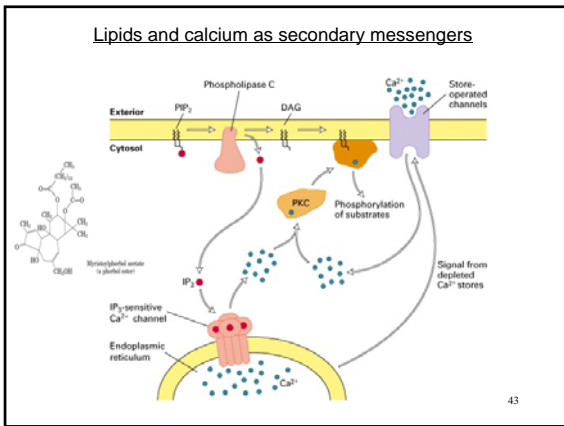


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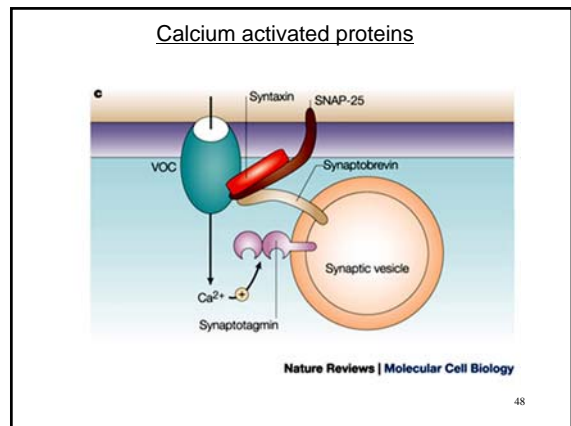
### Glucose metabolism controlled by Insulin signaling







- ### Calcium activated proteins
- Calmodulin: CaM kinase; phosphorylase b kinase (glycogen breakdown)
  - Protein kinase C
  - Calcineurin: protein phosphatase 1B
  - Troponin - muscle contraction
  - Synaptotagmin (neurotransmitter release)
  - Guanylyl cyclase
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**TABLE 20-4 Cellular Responses to Hormone-Induced Rise in Inositol 1,4,5-Triphosphate (IP<sub>3</sub>) and Subsequent Rise in Cytosolic Ca<sup>2+</sup> in Various Tissues**

Tissue	Hormone Inducing a Rise in IP <sub>3</sub>	Cellular Response
Pancreas (acinar cells)	Acetylcholine	Secretion of digestive enzymes, such as amylase and trypsinogen
Parotid (salivary gland)	Acetylcholine	Secretion of amylase
Pancreas (β cells of islets)	Acetylcholine	Secretion of insulin
Vascular or stomach smooth muscle	Acetylcholine	Contraction
Liver	Vasopressin	Conversion of glycogen to glucose
Blood platelets	Thrombin	Aggregation, shape change, secretion of hormones
Mast cells	Antigen	Histamine secretion
Fibroblasts	Peptide growth factors, such as bombesin and FGFβ	DNA synthesis, cell division
Sea urchin eggs	Spermatozoa	Rise of fertilization membrane

source: M. J. Berridge, 1987, *Ann. Rev. Biochem.* 56:159; M. J. Berridge and R. F. Irvine, 1984, *Nature* 312:315.

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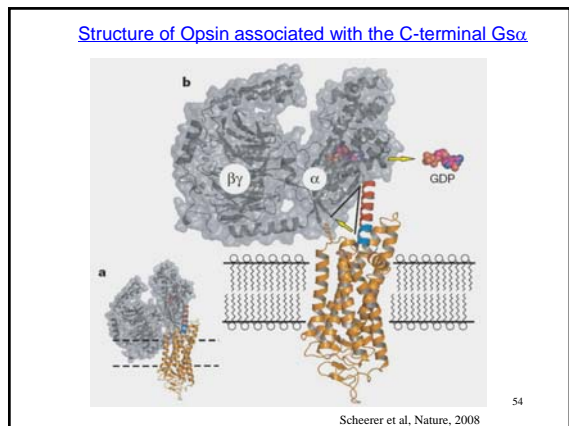
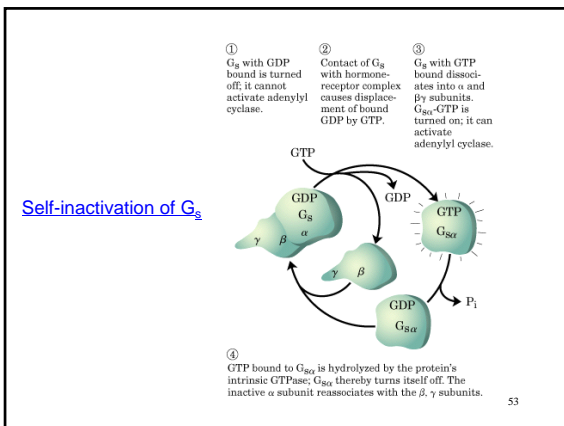
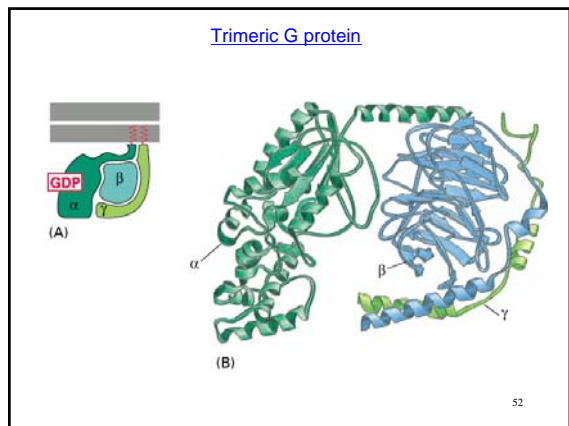
General introduction  
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 cGMP  
 Lipids  
 Calcium  
 G proteins  
 Trimeric G proteins  
 Monomeric G proteins, Tyr kinase/MAP kinase  
 Protein modules

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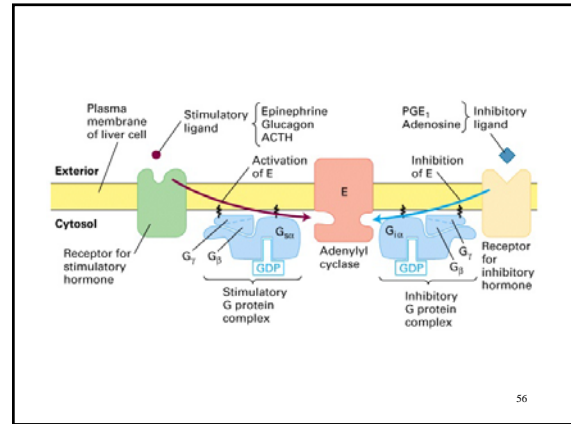
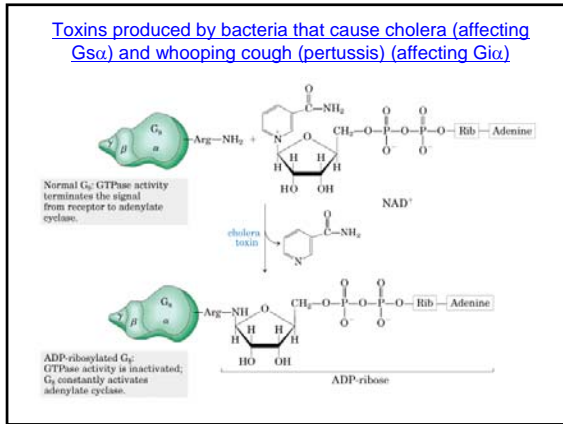
**GTP-binding proteins: A superfamily**

- Trimeric G proteins: G<sub>s</sub>, G<sub>i</sub>, G<sub>q</sub>, G<sub>t</sub>
- Small GTP-binding proteins
  - ✓ Ras: cell growth
  - ✓ Rac, Rho, Cdc42: cell migration
  - ✓ Rab: membrane trafficking
  - ✓ ARF: membrane trafficking
  - ✓ Ran: Nuclear transport
- Other GTP-binding proteins: Dynamin, EF-Tu

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**Toxins produced by bacteria that cause cholera (affecting  $G_{\alpha}$ ) and whooping cough (pertussis) (affecting  $G_{\alpha}$ )**



$G_{\alpha}$ Subclass*	Effect	Associated Effector Protein	2nd Messenger
$G_{\alpha_s}$	↑	adenylyl cyclase	cAMP
	↑	Ca <sup>2+</sup> channel	Ca <sup>2+</sup>
	↓	Na <sup>+</sup> channel	Change in membrane potential
$G_{\alpha_i}$	↓	adenylyl cyclase	cAMP
	↑	K <sup>+</sup> channel	Change in membrane potential
	↓	Ca <sup>2+</sup> channel	Ca <sup>2+</sup>
$G_{\alpha_q}$	↑	Phospholipase C	IP <sub>3</sub> , DAG
$G_{\alpha_{12}}$	↑	Phospholipase C	IP <sub>3</sub> , DAG
$G_{\alpha_{11}}$	↓	Ca <sup>2+</sup> channel	Ca <sup>2+</sup>
	↑	cGMP phosphodiesterase	cGMP
$G_{\alpha_{13}}$	↑	Phospholipase C	IP <sub>3</sub> , DAG
	↓	Adenylyl cyclase	cAMP

\*A given  $G_{\alpha}$  may be associated with more than one effector protein. To date, only one major  $G_{\alpha_s}$  has been identified, but multiple  $G_{\alpha_i}$  and  $G_{\alpha_q}$  proteins have been described. In some cases (not indicated in this table) effector proteins are regulated by coincident binding to  $G_{\alpha}$  and  $G_{\beta\gamma}$ .

key: ↑ = stimulation; ↓ = inhibition; IP<sub>3</sub> = inositol 1,4,5-trisphosphate; DAG = 1,2-diacetylgllycerol.

source: See A. G. Dolphin, 1987, *Trends Neurosci* 10:53; L. Birnbaumer, 1992, *Cell* 71:1069.

Family/subunit	Mass (kDa × 10 <sup>-3</sup> )	% Amino acid identity <sup>a</sup>	Toxin <sup>b</sup>	Tissue distribution	Representative receptors	Effector/role	
$G_{\alpha_s}$	$G_{\alpha_{s1}}$ (27)	44.2	100	CTX	Ubiquitous	BAR <sup>c</sup> , glucagon	↑ Adenylyl cyclase
	$G_{\alpha_{s2}}$	45.7	-	CTX	Ubiquitous	TSR, others	↑ Ca <sup>2+</sup> channels
	$G_{\alpha_{s3}}$	44.7	88	CTX	Olfactory neuro-epithelium	Olfactant	↑ Na <sup>+</sup> channels
$G_{\alpha_i}$	$G_{\alpha_{i1}}$	40.3	100	PTX	Nearly ubiquitous	M <sub>2</sub> Cho, $\alpha_2$ AR, others	↓ Adenylyl cyclase
	$G_{\alpha_{i2}}$	40.5	88	PTX	Ubiquitous	others	↑ Ca <sup>2+</sup> channels
	$G_{\alpha_{i3}}$	40.5	94	PTX	Nearly ubiquitous	others	↑ Adenylyl cyclase (?)
	$G_{\alpha_{i4}}$	40.0	73	PTX	Brain, others	Met-Enk, $\alpha_2$ AR, others	↑ Phospholipase C (?)
	$G_{\alpha_{i5}}$	40.1	73	PTX	Brain, others	others	↑ Phospholipase A <sub>2</sub> (?)
$G_{\alpha_q}$	$G_{\alpha_{q1}}$	40	68	CTX, PTX	Retinal rods	Rhodopsin	↑ cGMP-specific phosphodiesterase
	$G_{\alpha_{q2}}$	40.1	68	CTX, PTX	Retinal cones	Cone opsin	?
	$G_{\alpha_{q3}}$	40.5	67	CTX (?)	Taste buds	Taste (?)	?
$G_{\alpha_{12}}$	40.9	60	-	Brain, adrenal pituitary	M <sub>2</sub> Cho (?), others (?)	↓ Adenylyl cyclase (?)	
$G_{\alpha_{11}}$	$G_{\alpha_{11a}}$	42	100	-	Nearly ubiquitous	M <sub>2</sub> Cho, $\alpha_2$ AR, others	↑ Phospholipase C <sub>2</sub>
	$G_{\alpha_{11b}}$	42	88	-	Nearly ubiquitous	others	↑ Ca <sup>2+</sup> channels
	$G_{\alpha_{11c}}$	41.5	79	-	Lung, kidney, liver	?	↑ Phospholipase A <sub>2</sub> (?)
	$G_{\alpha_{11d}}$	43	57	-	B cells, myeloid cells	?	?
$G_{\alpha_{13}}$	43.5	58	-	T cells, myeloid cells	?	↑ Phospholipase C <sub>2</sub> , $\beta_2$ - $\beta_3$	
$G_{\alpha_{14}}$	$G_{\alpha_{14a}}$	44	100	-	Ubiquitous	?	?
	$G_{\alpha_{14b}}$	44	67	-	Ubiquitous	?	?

<sup>a</sup>% Amino acid identity: comparison is with the first-listed member of each family.

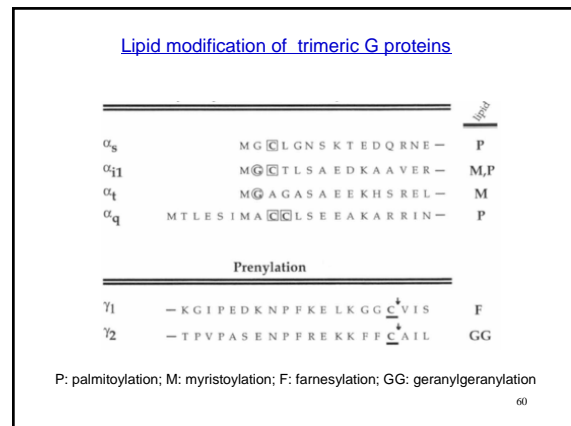
<sup>b</sup>Cholera toxin (CTX) and pertussis toxin (PTX) catalyze the ADP-ribosylation of an Arg residue (CTX) and a Gln residue (PTX), respectively, of the indicated subunits.

<sup>c</sup>Since various  $G_{\alpha_{11}}$  short forms of  $G_{\alpha_{11}}$ ,  $G_{\alpha_{11a}}$ , long forms of  $G_{\alpha_{11}}$ .

<sup>d</sup>Receptor abbreviations: BAR,  $\beta$ -adrenergic; M<sub>2</sub>Cho, M<sub>2</sub> muscarinic cholinergic;  $\alpha_2$ AR,  $\alpha_2$ -adrenergic; met-enk, met-enkephalin; M<sub>2</sub>Cho, M<sub>2</sub> muscarinic cholinergic; M<sub>2</sub>Cho, M<sub>2</sub> muscarinic cholinergic.

Subunit	Mass (kDa × 10 <sup>-3</sup> )	% Amino acid identity <sup>a</sup>	Tissue distribution	Effector/role	
$\beta$	$\beta_1$	37.3	100	Ubiquitous	Required for $G_{\alpha}$ -receptor interaction
	$\beta_2$	37.3	90	Nearly ubiquitous	
	$\beta_3$	37.2	83	Nearly ubiquitous	
	$\beta_4$	37.2	89	Nearly ubiquitous	
$\gamma$	$\gamma_1$	8.4	100	Retina, other (?)	Modulate activation of certain adenylyl cyclases by $G_{\alpha_s}$ or calmodulin
	$\gamma_2$	7.9	38	Brain, adrenal, other (?)	
	$\gamma_3$	8.5	36	Brain, testis	
	$\gamma_4$	(?partial)	(34)	[Kidney, retina (?)]	
	$\gamma_5$	7.3	25	Liver, other (?)	
	$\gamma_6$	7.5	35	Brain, other (?)	
$\gamma$	$\gamma_7$	8.4	100	Retina, other (?)	Support of agonist-induced receptor phosphorylation and desensitization
	$\gamma_8$	7.9	38	Brain, adrenal, other (?)	

<sup>a</sup>% Amino acid identity: comparison is with the first-listed member of each family.



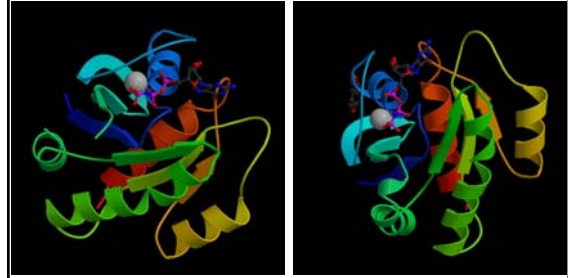
### Small GTP-binding proteins

- Ras: cell growth
- Rac, Rho, Cdc42: cell migration
- Rab: membrane trafficking
- ARF: membrane trafficking
- Ran: Nuclear transport

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### Ras

⚠ Oncogenes discovered from murine sarcoma viruses (Harvey virus - H-ras, Kirsten virus - K-ras) and N-ras;  
 ⚠ Activated in 10-50% of human tumors (G12V, Q61L, both of which are resistant to GAP).



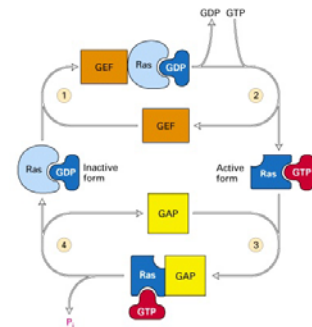
### Conserved motifs in Ras-like proteins

N-terminus 4-31aa	Guanine nucleotide binding domain 160 aa					Extension 13-49 aa	C-terminus
	PM1	G1	PM2	PM3	G2	G3	Caax xCC CxC
	GxxxxGKs	F	T	DxxG	nKxD	ExSA	

PM: phosphate/Mg<sup>2+</sup> binding regions; G: guanine base binding regions;  
 Caax: a=aliphatic, x= any residue

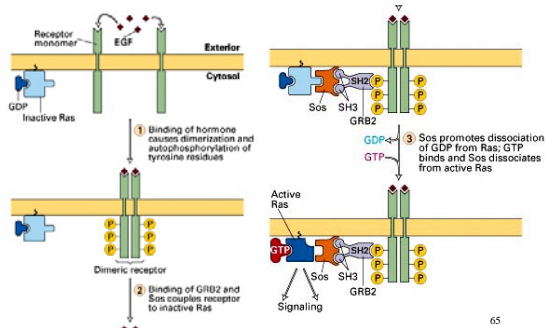
63

### The GTP/GDP cycle of small GTP-binding proteins



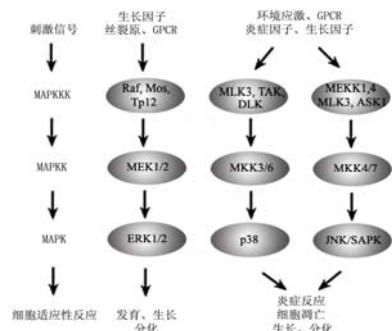
64

### Ras mediates signaling from Receptor Tyrosine Kinase (RTK)

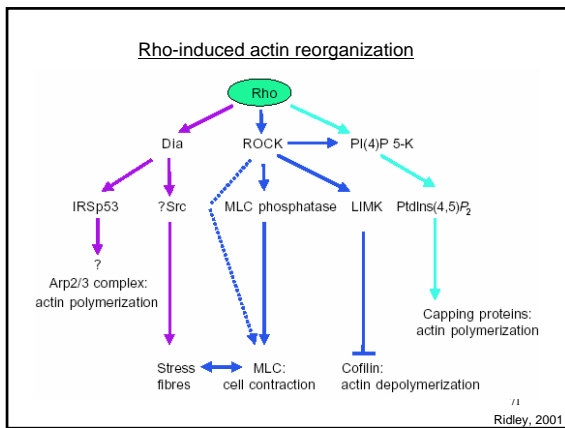
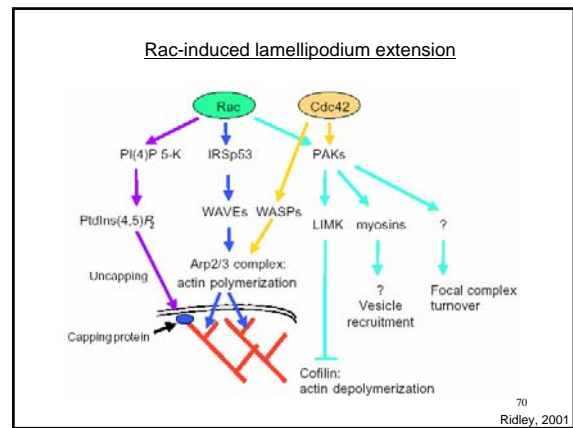
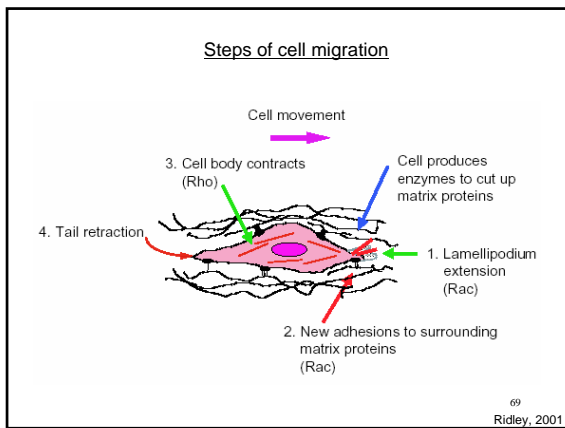
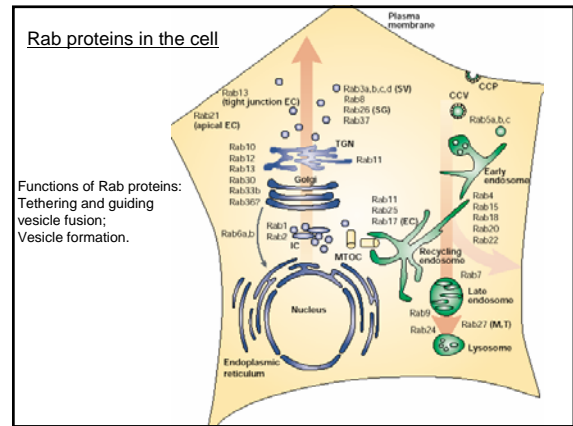
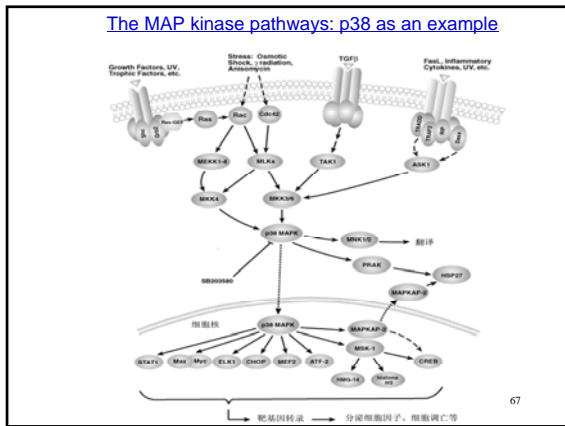


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### MAP kinase pathways



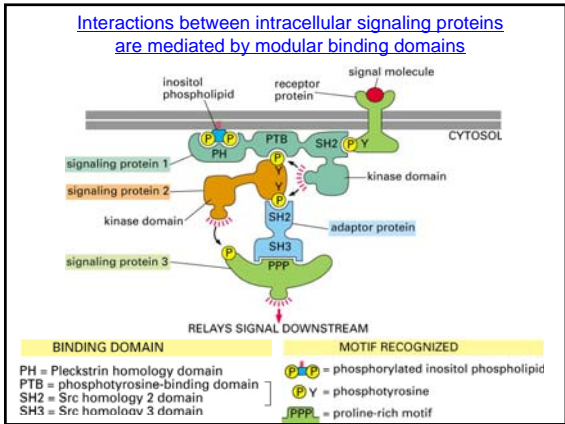
66



- General introduction
    - Common features of signal transduction
    - Cell surface signal transducers, receptors
  - Ion channels
  - Secondary messengers
    - cAMP
    - cGMP
    - Lipids
    - Calcium
  - G proteins
    - Trimeric G proteins
    - Monomeric G proteins, Tyr kinase/MAP kinase
  - Protein modules
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# Protein Modules: protein building blocks

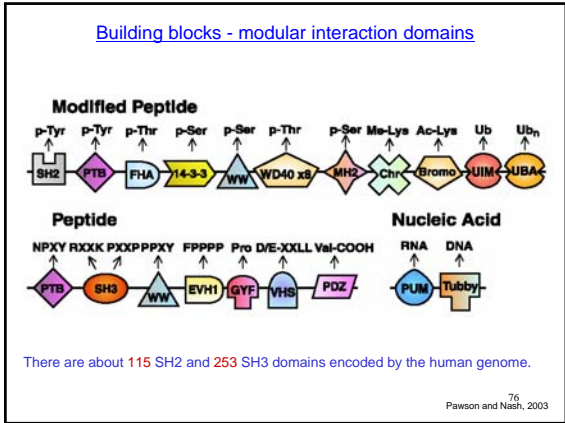
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### Protein modules

PTB domains: ~ 100-150 aa, bind to NPXY motifs: Shc, IRS-1  
 PDZ domains: ~80-90 aa, recognize short peptide motifs (4-5 residues) at the C-terminus of membrane proteins, usually containing a hydrophobic residue at the very end; protein-protein interaction: Dishevelled, FAP  
 SH2 (src homology): ~100 aa, binds to phosphotyrosine residues: Src, Grb2, Shc, STAT  
 SH3: binds to proline-rich sequences (PXXP): Src, Nck  
 WW domains: bind to Pro-rich sequences (XPPXY): Nedd4 (E3 ubiquitin ligase), Smurf, Dystrophin  
 Death domains: Fas  
 LIM domains: recognize turn-based motifs  
 PH (Pleckstrin-homology) domains: associate with phosphoinositides (PI<sub>3,4</sub>P<sub>2</sub>; PI<sub>4,5</sub>P<sub>2</sub>; PI<sub>3,4,5</sub>P<sub>3</sub>), target proteins to the plasma membrane: Akt, SOS  
 FYVE domains: associate with phosphoinositides (PI<sub>3</sub>P), target proteins to endosomes: EEA1, SARA

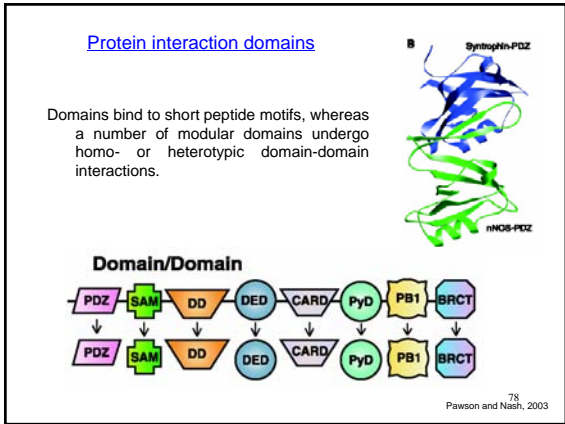
75



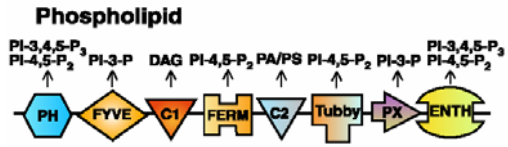
### Repeated motifs

Some interaction domains are assembled from repeated motifs (up to 50 copies): HEAT, TPR, Arm, ankyrin, leucine-rich, Pumilio repeat.

77  
Pawson and Nash, 2003

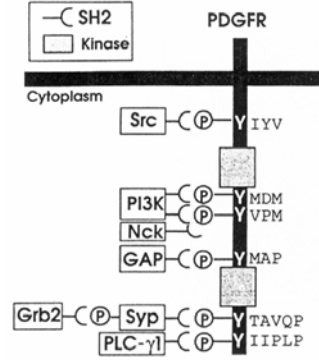


Protein-lipid interaction domains



79  
Pawson and Nash, 2003

Specificity of SH2 binding to phosphotyrosine



80  
Pawson, 1995

谢谢!

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