Chapter 13 - Biosignalling

table 13–1

Some Signals to Which Cells Respond
Antigens
Cell surface glycoproteins/oligosaccharides
Developmental signals
Extracellular matrix components
Growth factors
Hormones
Light
Mechanical touch
Neurotransmitters
Odorants
Pheromones
Tastants

Cells receive constant input from their environment

1

General feature of signal transmission

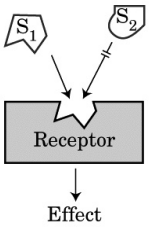
- Signal binds to receptor
- Activated receptor interacts with specific enzyme
- Activity of enzyme altered
- Change in metabolic activity
- Signal event terminated
- Cell returns to pre-stimulus event

2

Hallmarks of signal transduction mechanisms

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

Fig 13.1



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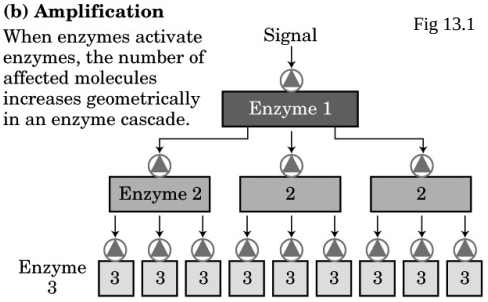
(b) Amplification
When enzymes activate enzymes, the number of affected molecules increases geometrically in an enzyme cascade.

Fig 13.1



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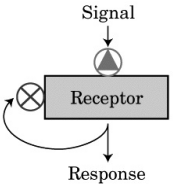
(c) Desensitization/Adaptation
Receptor activation triggers a feedback circuit that shuts off the receptor or removes it from the cell surface.

Fig 13.1



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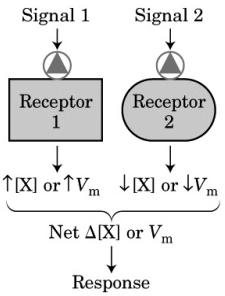
(d) Integration
When two signals have opposite effects on a metabolic characteristic such as the concentration of a second messenger X, or the membrane potential V_m, the regulatory outcome results from the integrated input from both receptors.

Fig 13.1



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Basic 4 signal transmission mechanisms

- Ion channels
- Receptor enzymes
- G protein-linked receptors
- Steroid hormones

Phosphorylation used by all cells to regulate cellular processes

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Gated ion channels

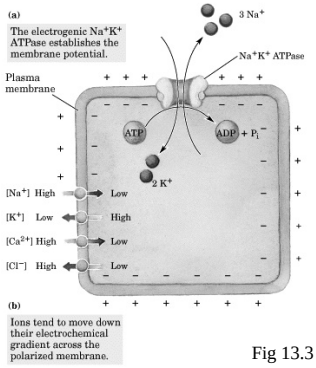

Fig 13.3

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Ligand-gated ion channel - Acetylcholine receptor

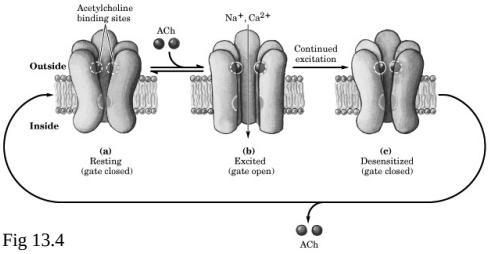

Fig 13.4

Binding of acetylcholine allows Na^+ and Ca^+ influx to depolarize membrane

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Voltage gated ion channels produce action potentials

Voltage sensitivity due to <u>charged</u> αα side chains

Ca^{2+} has both <u>passive</u> & <u>active</u> roles

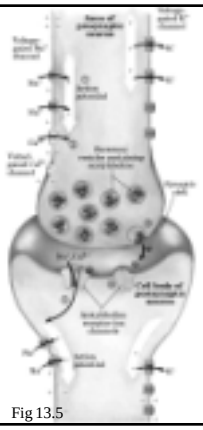

Fig 13.5

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Ion channels have other ligands beside acetylcholine

- Serotonin
- Glutamate
- Glycine (Cl^- channel)
- GABA

Anion channels are lined with <u>basic</u> αα side chains, cation channels with <u>acidic</u> side chains

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Receptor enzymes

- Ligand-binding domain on extracellular surface
- Catalytic site on cytosolic side
- Domains connected by transmembrane segment
- Receptor enzymes often protein kinases, guanylyl or adenylyl cyclases (NTP → cNMP)

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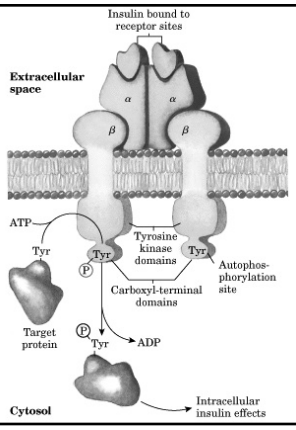
Example: the insulin receptor

A tyrosine-specific protein kinase



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Regulation of gene expression by insulin

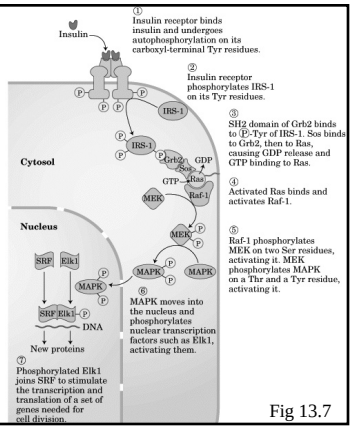

Fig 13.7

Activation of glycogen synthase by insulin

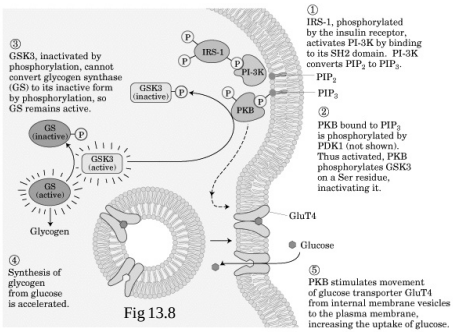

Fig 13.8

Phosphorylation & conversion of phosphatidylinositol 4,5 bisphosphate

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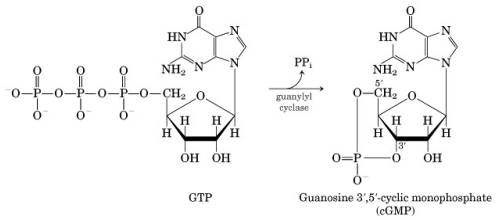
Receptor enzymes: Guanylyl cylcase



cGMP is a second messenger

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Guanylyl cyclase in signal transduction

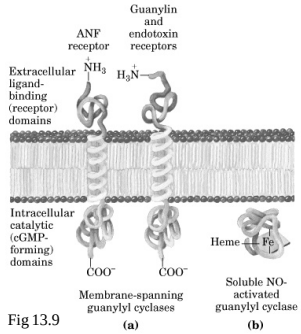

Fig 13.9

cGMP binding causes conformational change in PKG

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G protein-coupled receptors

3 essential components

- Plasma membrane receptor
  - 7 transmembrane segments
- GTP-binding protein
  - dissociates from receptor to enzyme
- Enzyme in plasma membrane
  - Generates cGMP, cAMP, phosphatidylinositol, Ca^{2+}

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Prototype = β-Adrenergic Receptor

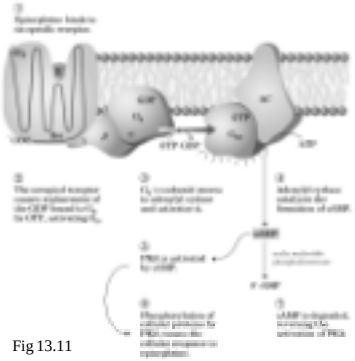


Fig 13.11

Stimulates production of cAMP

Stimulation by G_s is self-limiting

① G_s with GDP bound is turned off; it cannot activate adenylyl cyclase.

② Contact of G_s with hormone-receptor complex causes displacement of bound GDP by GTP.

③ G_s with GTP bound dissociates into α and βγ subunits. $G_{s\alpha}$-GTP is turned on; it can activate adenylyl cyclase.

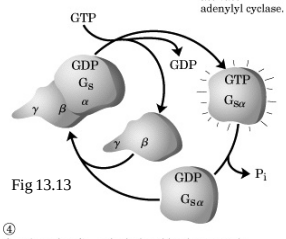
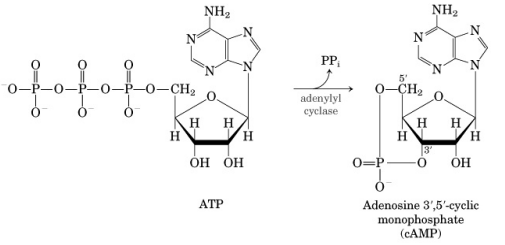


Fig 13.13

④ GTP bound to $G_{s\alpha}$ is hydrolyzed by the protein's intrinsic GTPase; $G_{s\alpha}$ thereby turns itself off. The inactive α subunit reassociates with the β, γ subunits.

G-proteins & Adenylyl cyclase



ATP

Adenosine 3′,5′-cyclic monophosphate (cAMP)

cAMP activation

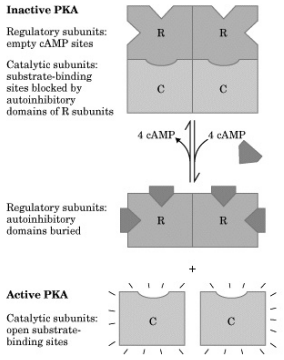


Fig 13.14 (a)

Epinephrine, G-proteins, cAMP & signal amplification

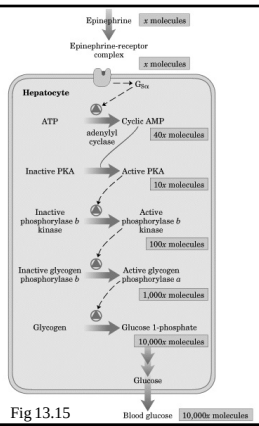


Fig 13.15

Enzymes regulated by cAMP-dependent phosphorylation

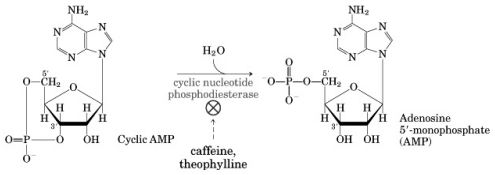
Table 13–3

Some Enzymes Regulated by cAMP-Dependent Phosphorylation (by PKA)

Enzyme	Sequence phosphorylated*	Pathway
Glycogen synthase	RASCTSSS	Glycogen synthesis
Phosphorylase *b* kinase	α subunit: VEFRRLSI	Glycogen breakdown
	β subunit: RTKRSGSV	
Pyruvate kinase (rat liver)	GVLRRASVAZL	Glycolysis
Pyruvate dehydrogenase complex (type L)	GYLRRASV	Pyruvate to acetyl-CoA
Hormone-sensitive lipase	PMRRSV	Triacylglycerol mobilization and fatty acid oxidation
Phosphofructokinase-2/fructose 2,6-bisphosphatase	LQRRRGSSIPQ	Glycolysis/gluconeogenesis
Tyrosine hydroxylase	FIGRRQSL	Synthesis of L-DOPA, dopamine, norepinephrine, and epinephrine
Histone H1	AKRKASGPPVS	DNA condensation
Histone H2B	KKAKASRKESYSVYVYK	DNA condensation
Cardiac phospholamban (a cardiac pump regulator)	AIRRAST	Regulation of intracellular $[Ca^{2+}]$
Protein phosphatase-1 inhibitor-1	IRRRRPTP	Regulation of protein dephosphorylation
CREB	ILSRRPSY	cAMP regulation of gene expression
PKA consensus sequence†	XR(R/K)X(S/T)B	

*The phosphorylated S or T residue is shown in red. All residues are given as their one-letter abbreviations (see Table 5–1).
†X is any amino acid; B is any hydrophobic amino acid.

cAMP is short-lived



Inhibited by caffe ine, theophylline (me thyl xanthines)

25

β-adrenergic re ceptor d esensitize d by phosphorylation

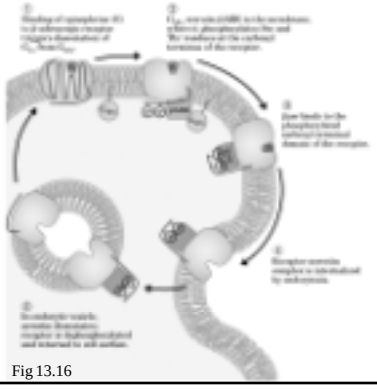


Fig 13.16

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Signals that use cAMP in signal transmission

table 13–4

Some Signals That Use cAMP as Second Messenger

- Corticotropin (ACTH)
- Corticotropin-releasing hormone (CRH)
- Dopamine [D-1, D-2]*
- Epinephrine (β-adrenergic)
- Follicle-stimulating hormone (FSH)
- Glucagon
- Histamine [H-2]*
- Luteinizing hormone (LH)
- Melanocyte-stimulating hormone (MSH)
- Odorants (many)
- Parathyroid hormone
- Prostaglandins E_1, E_2 (PGE_1, PGE_2)
- Serotonin [5-HT-1α, 5-HT-2]*
- Somatostatin
- Tastants (sweet, bitter)
- Thyroid-stimulating hormone (TSH)

*Some signals have two or more receptor subtypes (shown in square brackets), which may have different transduction mechanisms. For example, serotonin is detected in some tissues by receptor subtypes 5-HT-1a and 5-HT-1b, which act through adenylyl cyclase and cAMP, and in other tissues by receptor subtype 5-HT-1c, acting through the phospholipase C–IP_3 mechanism (see Table 13–5).

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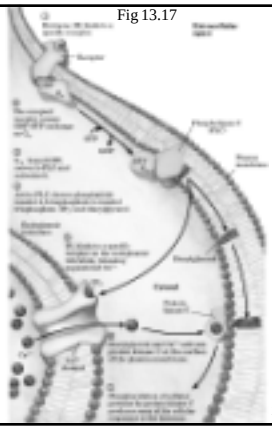
Other second messengers - phosphatidylinositol

Fig 13.17



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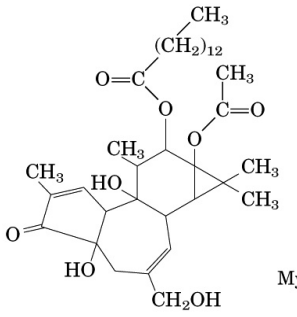
Protein Kinase C - target of tumor promoters



Myristoylphorbol acetate (a phorbol ester)

Uncontrolled phosphorylation

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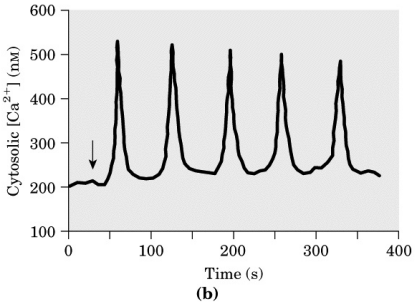
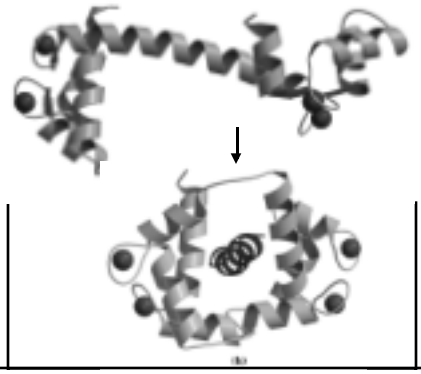
Ca^{2+} as a second messenger



Hormonal, neural, etc. response causes influx of Ca^{2+} into cell

30

Calmodulin modulates many Ca^{2+}-dependent responses



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Sensory transduction in Vision, Smell & Taste

- Gated ion channels
- Intracellular second messengers (cGMP,cAMP,Ca^{2+})
- Integration of input
- Desensitization

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Biochemistry of vision

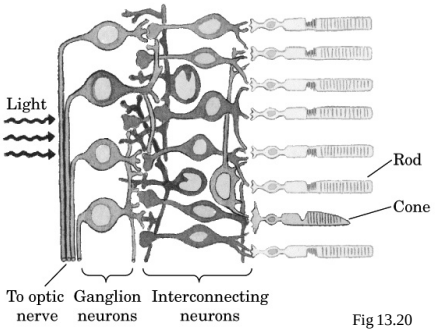

Fig 13.20

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General features of light-induced signalling

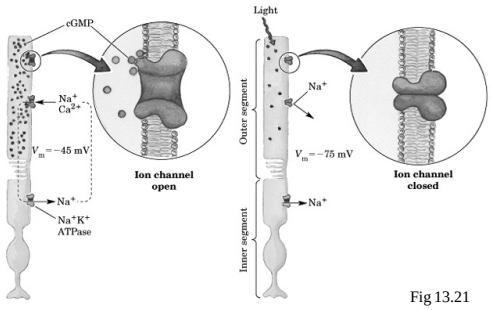

Fig 13.21

Hyperpolarization of membrane triggers signal

34

Detailed features of light-induced signalling

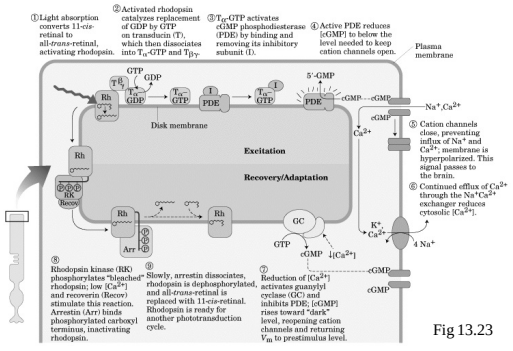

Fig 13.23

Decrease in [cGMP] causes ion channels to close

35

Recovery phase depends on ↑ [cGMP]

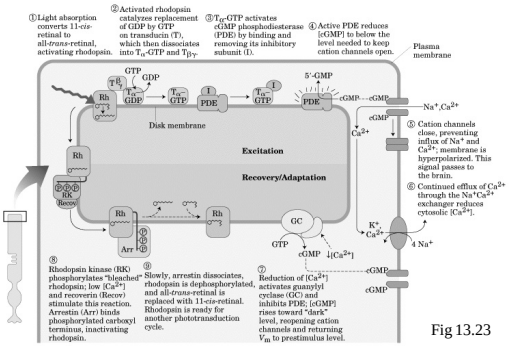

Fig 13.23

Low [Ca^{2+}] stimulates conversion of GTP → cGMP

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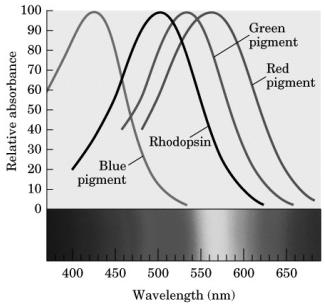
Cone cells & color vision



Different rhodopsins place chromophore (11-cis-retinal) in slightly different chemical environments

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The biochemistry of olfaction (smell)

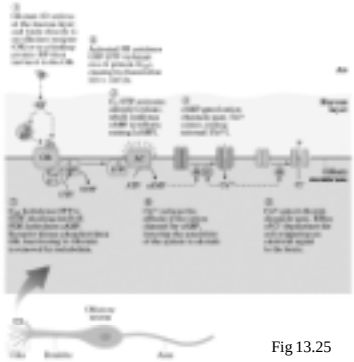

Fig 13.25

G-proteins stimulate cAMP production

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The biochemistry of gustation (taste)

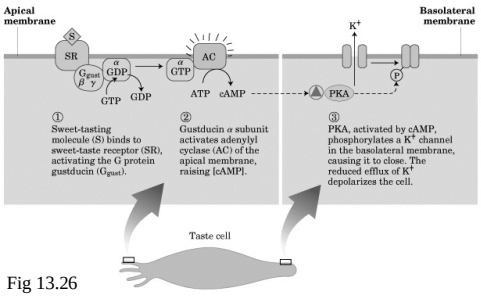

Fig 13.26

↑[cAMP] stimulates phosphorylation of K^+ channel

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Common features of signalling systems

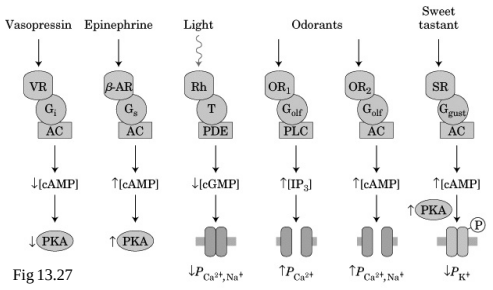

Fig 13.27

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Disruption of G-protein signalling & disease

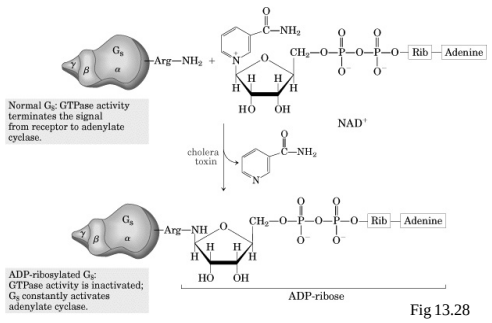

Fig 13.28

Choler & whooping cough toxins

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Regulation of gene expression by steroids

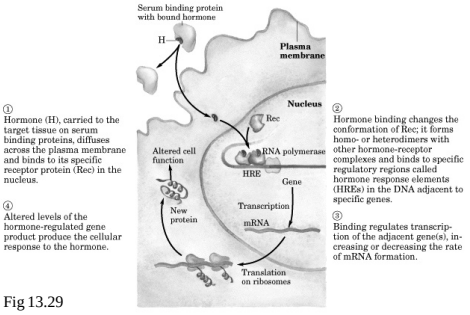

Fig 13.29

Bind to specific receptors in nucleus which then alter gene expression

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Phosphorylation as a regulatory mechanism

Means for Protein Kinase activation

- cGMP
- cAMP
- Insulin
- Ca^{2+}/calmodulin
- Ca^{2+}/ Diacylglycerol (DAG)
- Phosphorylation by other kinases

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Regulation of cell cycle by protein kinases

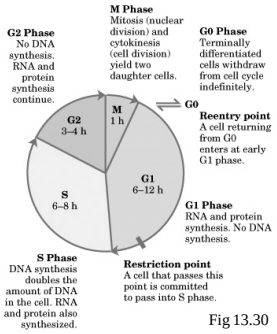

Fig 13.30

Phosphorylation central to timing mechanism

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Cyclin-dependent Protein Kinases (CDK's)

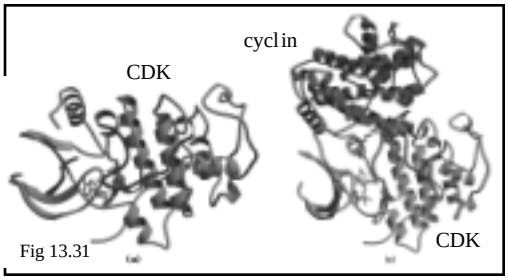

Fig 13.31

Active only in association with cyclin proteins

45

Activity of cyclin-CDK complexes strongly correlated with phases of cell cycle

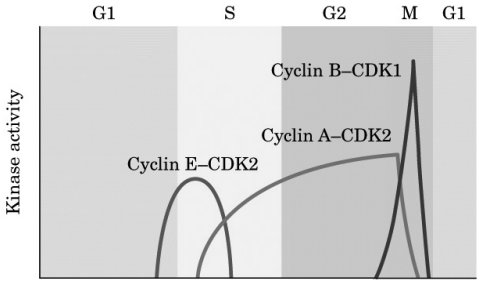

Fig 13.32

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4 mechanisms for regulating CDK activity

- Phosphorylation/dephosphorylation
- Controlled degradation of cyclins
- Controlled synthesis of CDK's & cyclins
- Specific CDK-inhibiting proteins

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Regulation of CDK's by phosphorylation

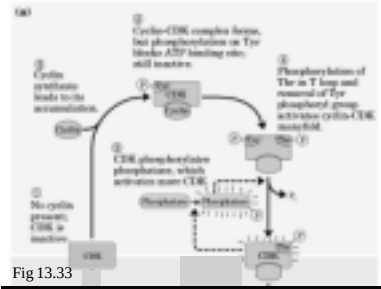

Fig 13.33

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Controlled degradation of cyclins

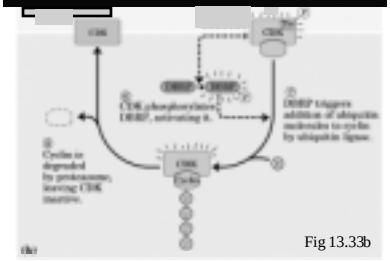
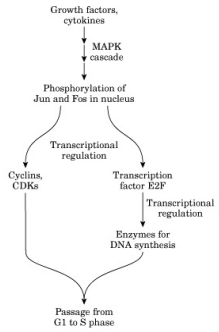


Fig 13.33b

Increased CDK activity increases cyclin breakdown

49

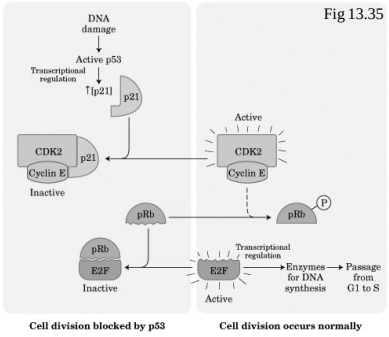
Regulated synthesis of CDK's & cyclins



Synthesized in response to growth factors & cytokines

50

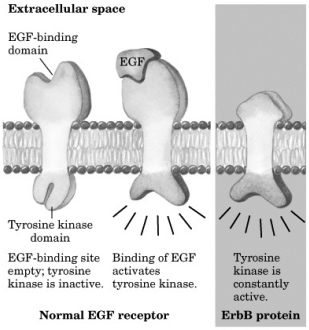
Inhibition of CDK's



Protein binding prevents cyclin-CDK action

51

Oncogenes



Mutant forms of genes that regulate the cell cycle

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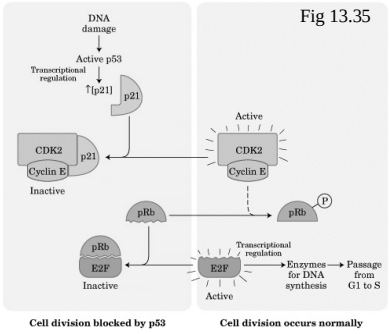
Tumor suppressor genes



Gene products that suppress cell cycle division

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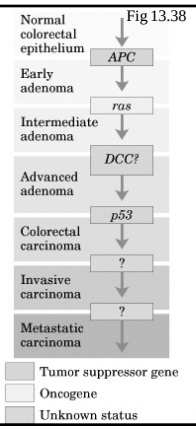
Mutation in an oncogene or tumor suppressor gene doesn't automatically lead to cancer

Accumulation of mutations required



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Apoptosis & Programmed cell death

- Embryonic development (fingers from limb buds)
- Defense against viral infection
- Selection against self-recognizing immune cells
- Defense against genetic mutations resulting from irradiation, chemical mutagenesis, etc.

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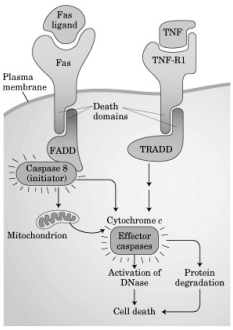
Apoptosis



"suicide" molecules & "death domains"

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Chapter 13 - Summary

Signal-transduction

- Specificity & affinity for chemical signal
- Amplification of signal
- Integration of input from multiple receptors
- Desensitization to response

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4 general signalling mechanisms

- Gated ion channels
  - Acetylcholine (ligand-gated)
  - Na^+, K^+, Cl^-, Ca^{2+} (Voltage-gated)
  - V_M across membrane due to differences in $[Na^+]$, $[K^+]$
- Receptor enzymes (insulin receptor)
  - Extracellular ligand-binding domain
  - Intracellular catalytic domain (kinase)

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- G-protein coupled receptors (β-adrenergic receptor)
  - Serpentine transmembrane receptors
  - G-protein exchange of GDP for GTP
  - Activated G-protein stimulates cyclases (cAMP, cGMP), phospholipases, kinases, etc.
  - Vision, taste & smell
- Steroid Hormones
  - Hydrophobic - don't require transmembrane receptor
  - Bind to nuclear proteins - alter gene expression

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- Second messengers
  - Intracellular signals generated in response to binding of ligands by receptors
  - cAMP, cGMP, Ca^{2+}, inositol 1,4,5-triphosphate (IP_3), diacylglycerol (DAG)
  - Bind to ion channels, kinases etc. to regulate V_m, phosphorylation of enzymes, $[Ca^{2+}]$, etc.

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- Progression of cell cycle controlled by a family of protein kinases (CDK's) bound to cyclins
- Regulation critical to progression
  - Differential synthesis of CDK's
  - Specific degradation of cyclin
  - Phosphorylation/dephosphorylation
  - Binding of inhibitory proteins

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- Oncogenes
  - Encode defective signalling proteins
  - Genetically dominant
  - Ex.'s: growth factors, receptors, G-proteins, kinases, etc.
- Tumor suppressor genes
  - Regulatory proteins that inhibit cell division
  - Genetically recessive
  - Ex.'s: Retinoblastoma protein (Rb), p53, p21 etc.
- Apoptosis
  - Programmed cell death in response to extracellular signal

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