

Advanced Cell Biology. Lecture 36

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Outline

Questions and answers

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G-protein-coupled receptors

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G-protein-coupled receptors

Enzyme-coupled receptors

What is the functional difference between α subunit and $\beta\gamma$ complex of GPCR?

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- 
- Minot State
-
- UNIVERSITY

Inositol phospholipid pathway

- ▶ Instead of adenylyl cyclase, some G proteins activate phospholipase C
- ▶ Phospholipase C cleaves inositol phospholipid present in the inner layer of membrane
- ▶ Vasopressin, acetylcholine and trombin activate this pathway

- ▶ Phospholipase C produces inositol 1,4,5-triphosphate (IP₃) and diacylglycerol (DAG)
- ▶ IP₃ activates Ca²⁺ channels in ER
- ▶ DAG activates protein kinase C (Ca²⁺ is needed)
- ▶ Both Ca²⁺ and PKC are signals to other proteins

Inositol 1,4,5-triphosphate (IP_3) signal pathway

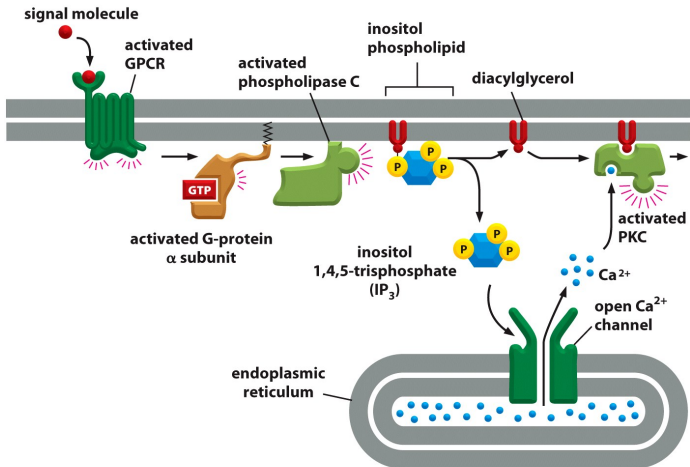


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Ca²⁺ signal

- ▶ Ca^{2+} is a frequent intracellular signal which signals egg to divide, muscle cell to contract etc.
- ▶ Normally, Ca^{2+} concentration is high both in ER and outer space

Calcium wave movie

- ▶ Calmodulin is a Ca^{2+} responsive protein
- ▶ It binds four Ca^{2+} ions and changes conformation, wrapping around target proteins
- ▶ Ca^{2+} /calmodulin-dependent protein kinases are activated by calmodulin and in turn start to phosphorylate other proteins (some CaMs are probably responsible for location memory)

Calmodulin

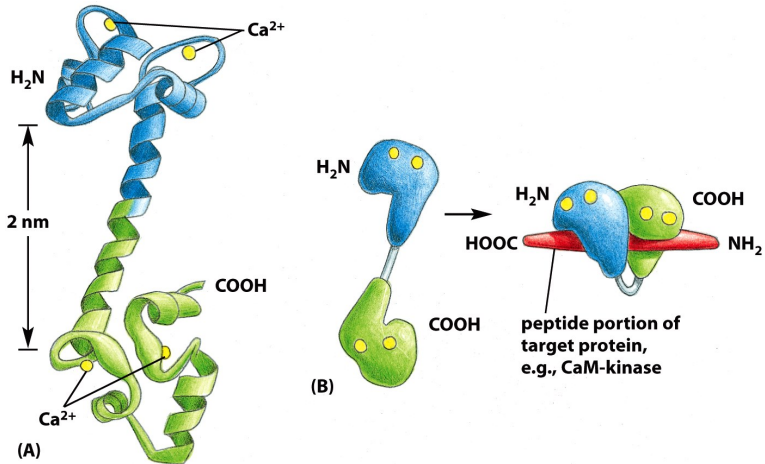


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Calmodulin movie

- ▶ Despite of complexity, could be very fast
- ▶ Allow amplification and adaptation

- ▶ Rhodopsin receptor activated transducin G protein
- ▶ α subunit of transducin activates hydrolysis of cyclic GMP and closing of cation channels
- ▶ On the bright light, amplification steps are inhibited and cascade adapts

Amplification in rhodopsin-transducin cascade

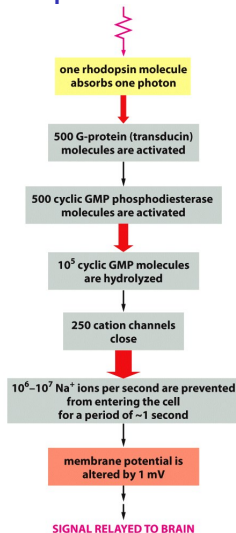


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EXTRACELLULAR SIGNAL MOLECULE*

TARGET TISSUE

MAJOR RESPONSE

increase in heart rate and force of contraction

skeletal muscle

glycogen breakdown

Adrenaline, ACTH, glucagon

fat

fat breakdown

ACTH

adrenal gland

cortisol secretion

SIGNAL MOLECULE

Vasopressin (a peptide hormone)

TARGET TISSUE

liver

MAJOR RESPONSE

glycogen breakdown

Acetylcholine

pancreas

**secretion of amylase
(a digestive enzyme)**

Acetylcholine

smooth muscle

contraction

Thrombin (a proteolytic enzyme)

blood platelets

aggregation

- ▶ Many of enzyme-coupled receptors have growth-related (growth, proliferation, differentiation) or movement-related functions
- ▶ Their signals are paracrine molecules which work at low concentrations
- ▶ Most of enzyme-coupled receptors have tyrosine kinase cytoplasmic domain (PKA, PKC and CaM are serine/threonine kinases): receptor tyrosine kinases (RTKs)

- ▶ Signal causes RTKs to form dimers which start to phosphorylate themselves
- ▶ Phosphorylated dimers are binding sites for many proteins, including direct signals and adaptors
- ▶ Protein tyrosine phosphatases or endosomes will stop dimers to produce a signal

Activation of RTK

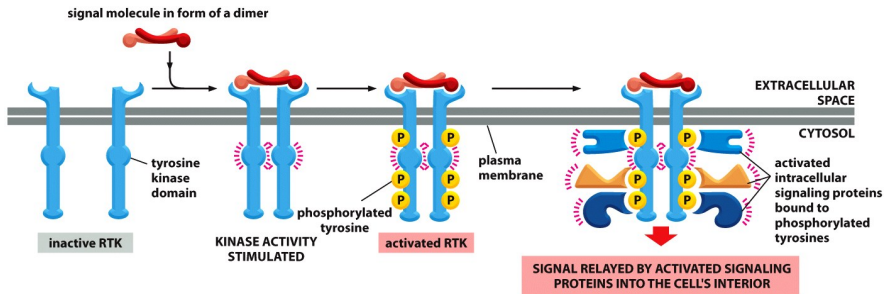


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- ▶ Ras is a monomeric GTPase, similar to α subunit of G protein
- ▶ Ras is activated through adaptor and Ras-activating proteins which bind GTP to it
- ▶ Ras is then hydrolyze GTP into GDP and became inactive again

Activation of Ras

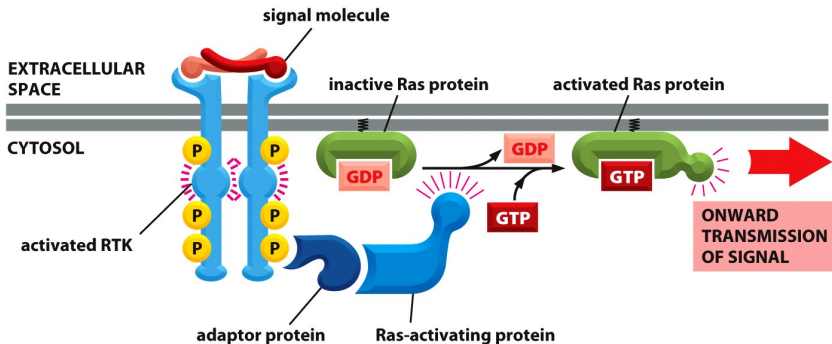


Figure 16-31 Essential Cell Biology 3/e (© Garland Science 2010)

Ras movie

- ▶ Active Ras may activate mitogen-activated protein kinase module (MAP-kinase module)
- ▶ MAP kinase will change gene expression and protein activity which may result in cell proliferation
- ▶ MAP kinase is activated by MAP kinase kinase which is activated by MAP kinase kinase kinase which is activated by active Ras
- ▶ Some cancers are related with inability of activated Ras to hydrolyze its own GTP

MAP kinase pathway

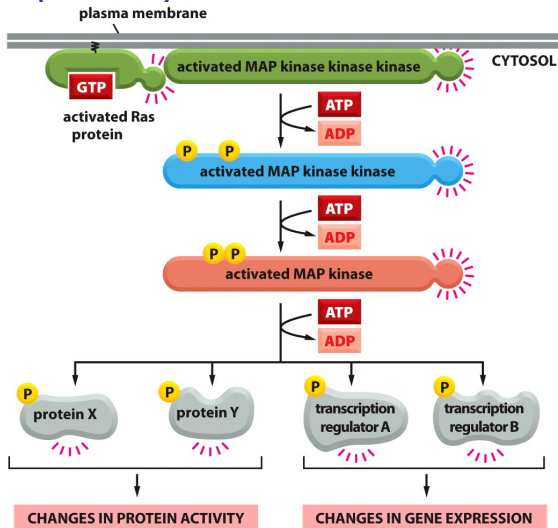


Figure 16-32 Essential Cell Biology 3/e (© Garland Science 2010)

Final question (1 point)

What is the main function of calmodulin?

- ▶ Inositol phospholipid pathway involves PKC and Ca^{2+} instead of PKA; separate Ca^{2+} pathway involves CaM-kinases
- ▶ Many enzyme-coupled receptors are tyrosine kinases (RTKs) which phosphorylate themselves
- ▶ Constant activation of MAP-kinase signaling module by Ras leads to many human cancers

For Further Reading



A. Shipunov.

Advanced Cell Biology [Electronic resource].

2011—onwards.

Mode of access: [http:](http://)

[//ashipunov.info/shipunov/school/biol_250](http://ashipunov.info/shipunov/school/biol_250).



B. Alberts et al.

Essential Cell Biology. 3rd edition.

Garland Science, 2009.

Chapter 16: 551–558.