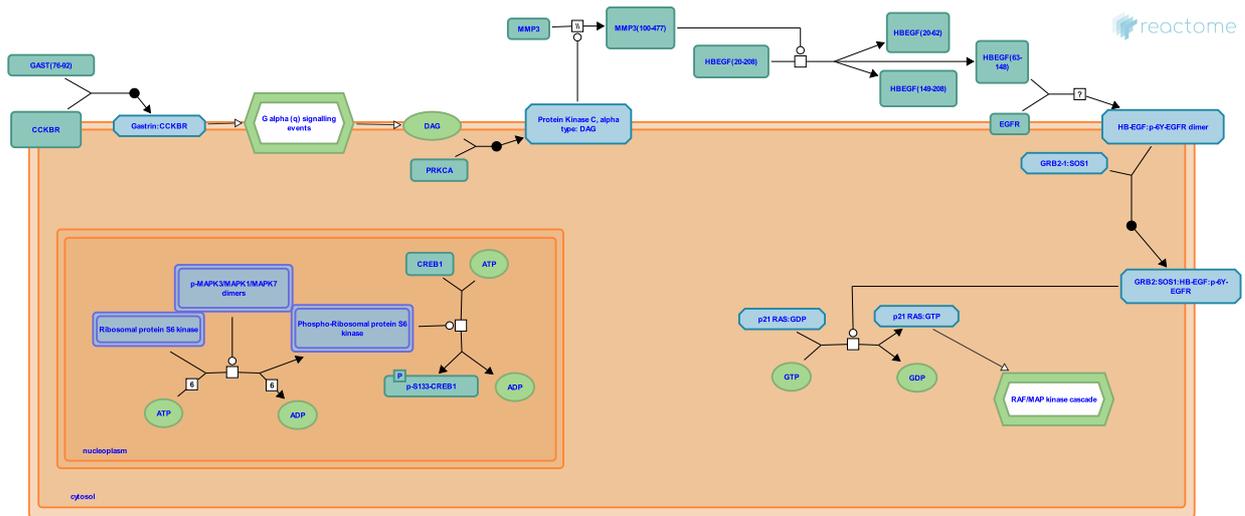


Gastrin-CREB signalling pathway via PKC and MAPK



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

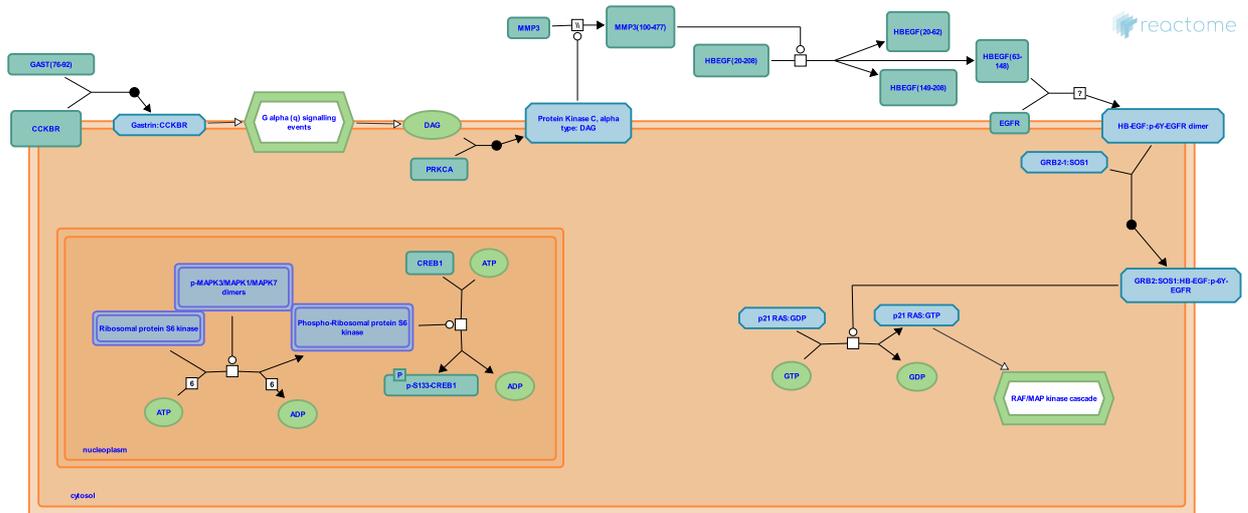
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Reactome database release: 81

This document contains 2 pathways and 3 reactions ([see Table of Contents](#))

Gastrin-CREB signalling pathway via PKC and MAPK ↗

Stable identifier: R-HSA-881907



Gastrin is a hormone whose main function is to stimulate secretion of hydrochloric acid by the gastric mucosa, which results in gastrin formation inhibition. This hormone also acts as a mitogenic factor for gastrointestinal epithelial cells. Gastrin has two biologically active peptide forms, G34 and G17. Gastrin gene expression is upregulated in both a number of pre-malignant conditions and in established cancer through a variety of mechanisms. Depending on the tissue where it is expressed and the level of expression, differential processing of the polypeptide product leads to the production of different biologically active peptides. In turn, acting through the classical gastrin cholecystokinin B receptor CCK-BR, its isoforms and alternative receptors, these peptides trigger signalling pathways which influence the expression of downstream genes that affect cell survival, angiogenesis and invasion (Wank 1995, de Weerth et al. 1999, Grabowska & Watson 2007)

Literature references

- Watson, SA., Grabowska, AM. (2007). Role of gastrin peptides in carcinogenesis. *Cancer Lett*, 257, 1-15. ↗
- Bläker, M., de Weerth, A., von Schrenck, T. (1999). [Receptors for cholecystokinin and gastrin]. *Z Gastroenterol*, 37, 389-401. ↗
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Editions

2012-04-04	Authored, Edited	Jassal, B., Tripathi, S.
2012-04-23	Reviewed	D'Eustachio, P.

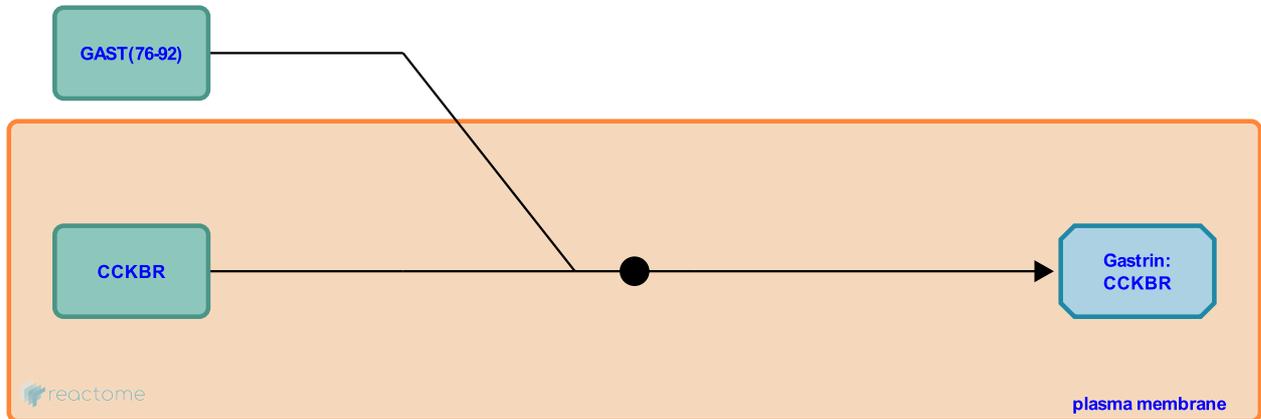
Gastrin binds to CCK-B receptor ↗

Location: [Gastrin-CREB signalling pathway via PKC and MAPK](#)

Stable identifier: R-HSA-870269

Type: binding

Compartments: plasma membrane, extracellular region



Gastrin receptors (gastric cholecystokinin B receptor, CCK-BR) mediate acid secretion from parietal cells, release of histamine from enterochromaffin-like (ECL) cells and contraction of smooth muscle (Ito et al. 1993). The hormone gastrin is the central regulator of gastric acid secretion and in addition, plays a prominent role in regulation of growth and differentiation of gastric and colonic mucosa.

Literature references

Chiba, T., Taniguchi, T., Tsukamoto, T., Murayama, T., Matsui, T., Nakata, H. et al. (1993). Functional characterization of a human brain cholecystokinin-B receptor. A trophic effect of cholecystokinin and gastrin. *J Biol Chem*, 268, 18300-5. ↗

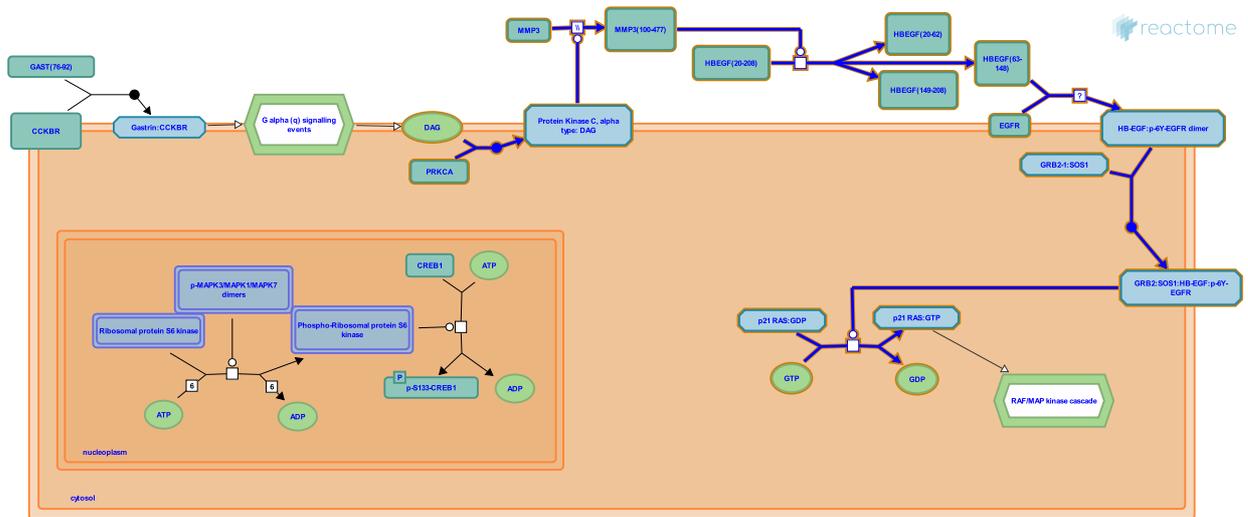
Editions

2012-04-04	Authored, Edited	Jassal, B., Tripathi, S.
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EGFR Transactivation by Gastrin ↗

Location: Gastrin-CREB signalling pathway via PKC and MAPK

Stable identifier: R-HSA-2179392



Gastrin, through the action of diacylglycerol produced from downstream G alpha (q) events, transactivates EGFR via a PKC-mediated pathway by activation of MMP3 (Matrix Metalloproteinase 3) which allows formation of mature HBEGF (heparin-binding epidermal growth factor) by cleaving pro-HBEGF. Mature HBEGF is then free to bind the EGFR, resulting in EGFR activation (Dufresne et al. 2006, Liebmann 2011).

Literature references

Liebmann, C. (2011). EGF receptor activation by GPCRs: an universal pathway reveals different versions. *Mol Cell Endocrinol*, 331, 222-31. ↗

Fourmy, D., Dufresne, M., Seva, C. (2006). Cholecystokinin and gastrin receptors. *Physiol Rev*, 86, 805-47. ↗

Editions

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2012-04-23	Reviewed	D'Eustachio, P.

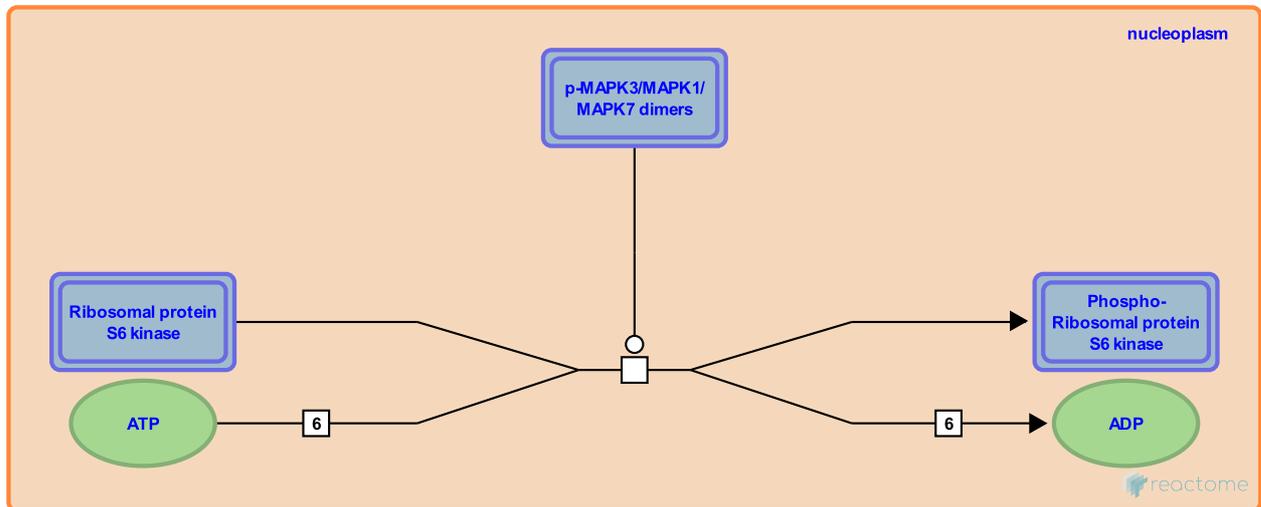
ERK1/2/5 activate RSK1/2/3 ↗

Location: [Gastrin-CREB signalling pathway via PKC and MAPK](#)

Stable identifier: R-HSA-198746

Type: transition

Compartments: nucleoplasm



The p90 ribosomal S6 kinases (RSK1-4) comprise a family of serine/threonine kinases that lie at the terminus of the ERK pathway. RSK family members are unusual among serine/threonine kinases in that they contain two distinct kinase domains, both of which are catalytically functional. The C-terminal kinase domain is believed to be involved in autophosphorylation, a critical step in RSK activation, whereas the N-terminal kinase domain, which is homologous to members of the AGC superfamily of kinases, is responsible for the phosphorylation of all known exogenous substrates of RSK.

RSKs can be activated by the ERKs (ERK1, 2, 5) in the cytoplasm as well as in the nucleus, they both have cytoplasmic and nuclear substrates, and they are able to move from nucleus to cytoplasm. Efficient RSK activation by ERKs requires its interaction through a docking site located near the RSK C terminus. The mechanism of RSK activation has been studied mainly with regard to ERK1 and ERK2. RSK activation leads to the phosphorylation of four essential residues Ser239, Ser381, Ser398, and Thr590, and two additional sites, Thr377 and Ser749 (the amino acid numbering refers to RSK1). ERK is thought to play at least two roles in RSK1 activation. First, activated ERK phosphorylates RSK1 on Thr590, and possibly on Thr377 and Ser381, and second, ERK brings RSK1 into close proximity to membrane-associated kinases that may phosphorylate RSK1 on Ser381 and Ser398.

Moreover, RSKs and ERK1/2 form a complex that transiently dissociates upon growth factor signalling. Complex dissociation requires phosphorylation of RSK1 serine 749, a growth factor regulated phosphorylation site located near the ERK docking site. Serine 749 is phosphorylated by the N-terminal kinase domain of RSK1 itself. ERK1/2 docking to RSK2 and RSK3 is also regulated in a similar way. The length of RSK activation following growth factor stimulation depends on the duration of the RSK/ERK complex, which, in turn, differs among the different RSK isoforms. RSK1 and RSK2 readily dissociate from ERK1/2 following growth factor stimulation, but RSK3 remains associated with active ERK1/2 longer, and also remains active longer than RSK1 and RSK2.

Followed by: [RSK1/2/3 phosphorylates CREB at Serine 133](#)

Literature references

Blenis, J., Richards, SA., Roux, PP. (2003). Phosphorylation of p90 ribosomal S6 kinase (RSK) regulates extracellular signal-regulated kinase docking and RSK activity. *Mol Cell Biol*, 23, 4796-804. [↗](#)

Ranganathan, A., Cobb, MH., Sturgill, TW., Pearson, GW., Chrestensen, CA. (2006). The MAP kinase ERK5 binds to and phosphorylates p90 RSK. *Arch Biochem Biophys*, 449, 8-16. [↗](#)

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
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2013-07-15	Edited	D'Eustachio, P., Matthews, L.

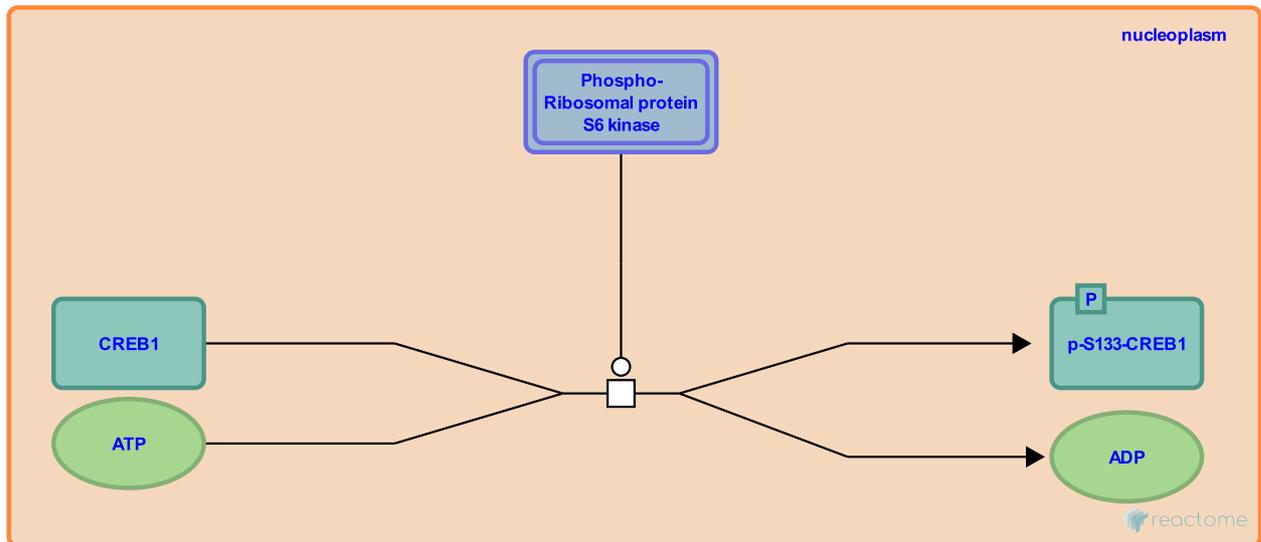
RSK1/2/3 phosphorylates CREB at Serine 133 [↗](#)

Location: [Gastrin-CREB signalling pathway via PKC and MAPK](#)

Stable identifier: R-HSA-199895

Type: transition

Compartments: nucleoplasm



CREB is phosphorylated at Serine 133 by RSK1/2/3.

Preceded by: [ERK1/2/5 activate RSK1/2/3](#)

Literature references

Jacquot, S., Hanauer, A., De Cesare, D., Sassone-Corsi, P. (1998). Rsk-2 activity is necessary for epidermal growth factor-induced phosphorylation of CREB protein and transcription of c-fos gene. *Proc Natl Acad Sci U S A*, 95, 12202-7. [↗](#)

Editions

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