reactome

MAP2Ks and MAPKs bind to the activated RAF complex

Roskoski, R Jr., Rothfels, K.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

18/10/2019

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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

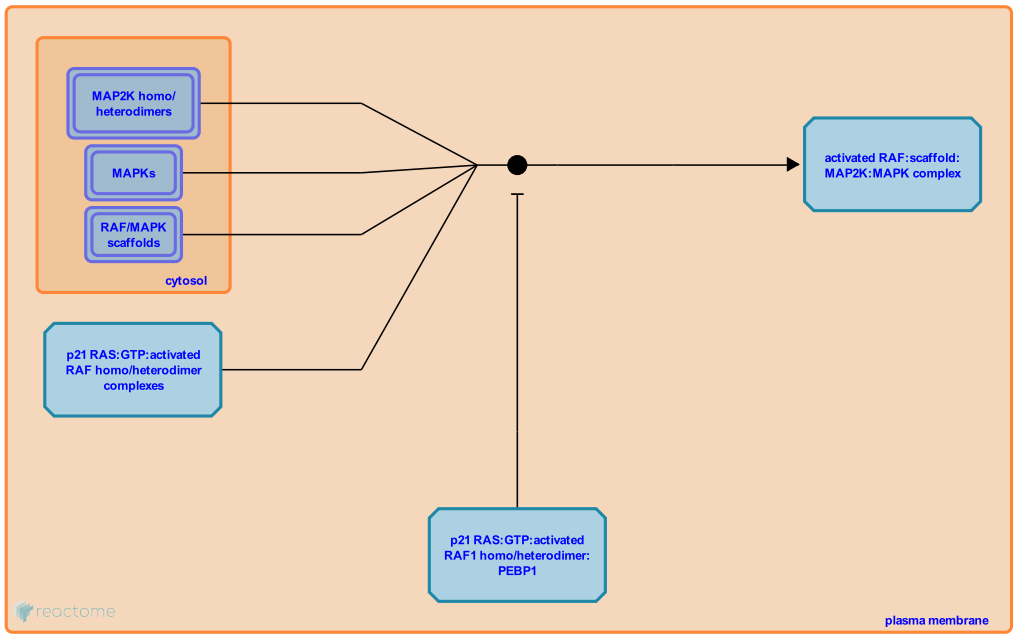
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

MAP2Ks and MAPKs bind to the activated RAF complex ↗

Stable identifier: R-HSA-5672972

Type: binding

Compartments: plasma membrane



RAF kinases have restricted substrate specificity and have as their primary substrates the two MAP2K proteins MAP2K1 and MAP2K2 (also known as MEK1 and 2). MAP2K1 knockout is embryonic lethal in mice, while MAP2K2 knockouts have no apparent abnormalities, suggesting that MAP2K1 can compensate for MAP2K2 in vivo (Giroux et al, 1999; Belanger et al, 2003). MAP2K proteins exist as stable homo- and heterodimers independent of growth factor stimulation and are generally recruited to activated RAF proteins in conjunction with a scaffolding protein and the MAP2K substrates, MAPK1 and 3 (also known as ERK1 and 2) (Ohren et al, 2004; Catalanotti et al, 2009; Catling et al, 1995; reviewed in Matallanas et al, 2011; Roskoski et al, 2012a; Roskoski et al, 2012b).

Scaffolding proteins promote signaling by providing a docking platform that colocalizes components of the signaling cascade, and provide specificity by controlling the spatial and temporal regulation of the pathway (reviewed in Brown and Sacks, 2009; Matallanas et al, 2011). KSR1 and 2, CNKSR1 and 2, IQGAP1 and the beta arrestins are among the known MAPK scaffold proteins that act at the plasma membrane upon MAPK pathway activation; in addition, paxillin localizes MAPK pathway components to focal adhesion sites in the plasma membrane (Roy et al, 2005; Ren et al, 2007; DeFea et al, 2000; Togho et al, 2003; Ishibe et al, 2003; reviewed in Claperon and Therrien, 2007; Brown and Sacks, 2009; Matallanas et al, 2011). Although this reaction depicts these scaffolding proteins acting equivalently, the details of how they promote pathway activation vary. For instance, KSR1 and 2 are constitutively bound to MAP2K dimers but recruit MAPKs only upon pathway stimulation, while IQGAP1 associates constitutively with both MAP2K and MAPK proteins in unstimulated cells and shows increased interaction with MAP2K1 upon pathway activation by EGF (Stewart et al, 1999; Cacace et al, 2000; Muller et al, 2000; Roy et al, 2004; Roy et al, 2005; reviewed in Brown and Sacks, 2009). Scaffolding complexes may be particularly important for the phosphorylation of cytosolic MAPK targets (reviewed in Casar et al, 2009).

Literature references

Casar, B., Pinto, A., Crespo, P. (2009). ERK dimers and scaffold proteins: unexpected partners for a forgotten (cytoplasmic) task. *Cell Cycle, 8*, 1007-13. ↗

Roskoski, R Jr. (2012). MEK1/2 dual-specificity protein kinases: structure and regulation. *Biochem. Biophys. Res. Commun., 417*, 5-10. ↗

Brown, MD., Sacks, DB. (2009). Protein scaffolds in MAP kinase signalling. *Cell. Signal., 21*, 462-9. ↗

Ishibe, S., Joly, D., Zhu, X., Cantley, LG. (2003). Phosphorylation-dependent paxillin-ERK association mediates hepatocyte growth factor-stimulated epithelial morphogenesis. *Mol. Cell, 12*, 1275-85. ↗

Catalanotti, F., Reyes, G., Jesenberger, V., Galabova-Kovacs, G., de Matos Simoes, R., Carugo, O. et al. (2009). A Mek1-Mek2 heterodimer determines the strength and duration of the Erk signal. *Nat. Struct. Mol. Biol., 16*, 294-303. ↗

Editions

2014-12-18	Authored	Rothfels, K.
2015-02-12	Edited	Rothfels, K.
2015-04-28	Reviewed	Roskoski, R Jr.