Report for Pathway Review

Introduction

This report is intended for reviewers of the pathway "RAF/MAP kinase cascade". It has been automatically generated.

Please Note:

* non-ASCII characters (primarily in author names) are not displayed correctly in this document. We apologize for this inconvenience.

* Each reaction description in this report starts with a reaction diagram that shows the input and output molecules for that reaction, any catalysts and regulators, and that lists the reactions that immediately precede and follow it.

* The description of any human reaction that has been inferred from a reaction in another species is followed (in the text) by a description of the corresponding reaction in that other species. These are referred to as "Source" reactions in this document. A more detailed description of the human reaction can be found by following the hyperlink to the corresponding webpage.

* You may come across overlapping/redundant information in the text summaries of the events. We include this redundancy to accommodate users who are not reading the module through as a chapter but rather coming to the website to visit individual pages. Each summary is meant to provide some context. We realize that this is not optimal for the person who happens to be reading the module as a chapter, but we try to strike a balance. Any suggestions for improvement are welcome.

* Our reference list is not necessarily complete. For each reaction, we aim to provide at least one primary literature reference that demonstrates the occurrence of a given reaction in humans. We unfortunately do not have the resources to identify all relevant references, but we would be happy to cite any that you feel should be included.

Review of text document

In your review, we would appreciate it if you could verify that the events that we describe (pathways and reactions) are annotated clearly and that the molecular details of the reactions are accurate.

Review of Website Pathway Browser

A more detailed description of the pathway as well as a pathway diagram can be found on our website. We would appreciate your feedback on the content of the website and its navigability as well. A link to a short tutorial of the pathway browser can be found at the top of the web page. The zoomable pathway diagram is interactive. Text descriptions are revealed in the panel below the diagram under the overview tab. To view a text description, select a participating molecules or reaction node in the diagram. Clicking on an event in the hierarchy in the left panel will highlight the event(s) in the diagram and a text description will be displayed in the panel below.

A more detailed description the website and its features can be found in our Users Guide.

*Note that the "Expression" and "Structure" data are not available before public release as it is provided by external resources.

1 RAF/MAP kinase cascade (Pathway)

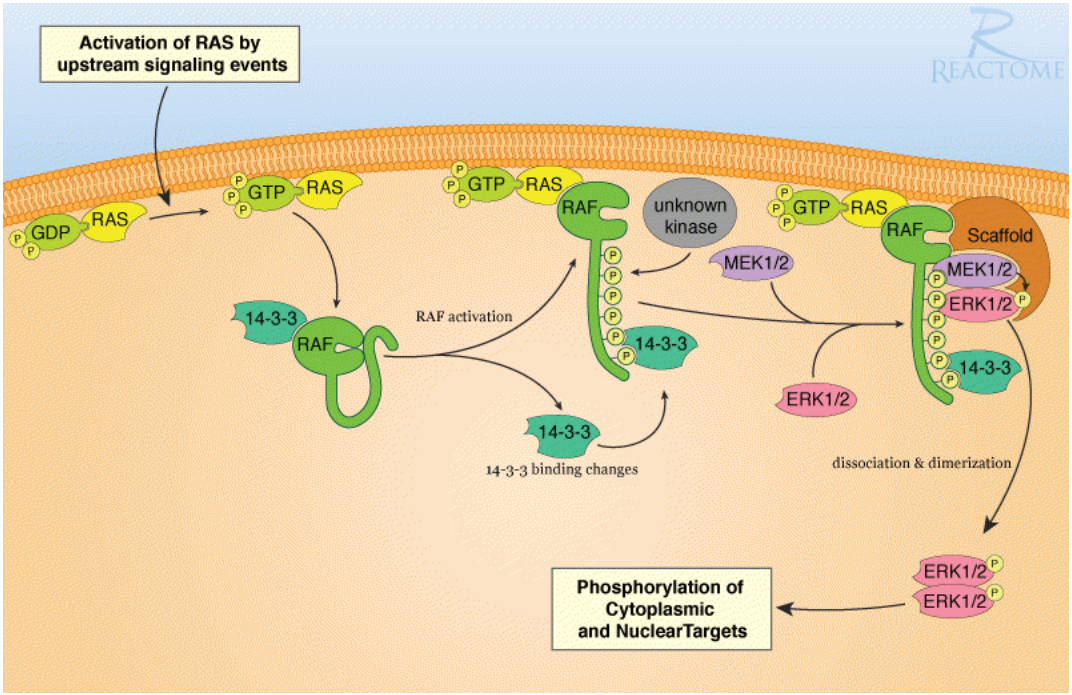
Authors

Charalambous, M, 2004-04-29 09:21:24.

Reviewers

Greene, LA, 2007-11-08 15:39:37.

The MAP kinase cascade describes a sequence of phosphorylation events involving serine/threonine-specific protein kinases. Used by various signal transduction pathways, this cascade constitutes a common 'module' in the transmission of an extracellular signal into the nucleus.



References

McKay MM, Morrison DK, "Integrating signals from RTKs to ERK/MAPK", Oncogene, 26, 2007, 3113-21.

Wellbrock C, Karasarides M, Marais R, "The RAF proteins take centre stage", Nat Rev Mol Cell Biol, 5, 2004, 875-85.

1.1 RAF activation (Pathway)

Authors

Charalambous, M, 2004-04-29 09:21:24.

Reviewers

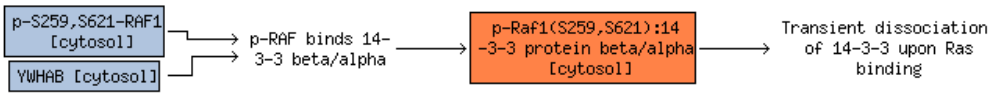
Greene, LA, 2007-11-08 15:39:37.

Phosphorylated RAF is activated by Ras binding and stabilised in its active form by transient disassociation and reassociation of 14-3-3, as well as further phosphorylation.

References

Morrison DK, Cutler RE, "The complexity of Raf-1 regulation.", Curr Opin Cell Biol, 9, 1997, 174-9.

1.1.1 p-RAF binds 14-3-3 beta/alpha (Reaction)



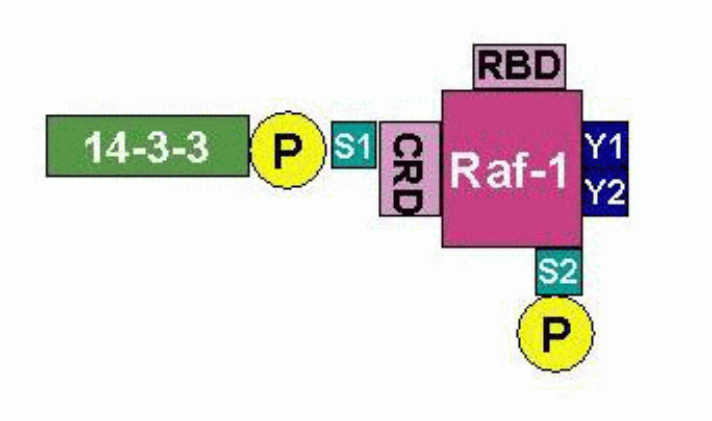
Authors

Charalambous, M, 2005-01-07 11:17:43.

Editors

Schmidt, EE, 0000-00-00 00:00:00.

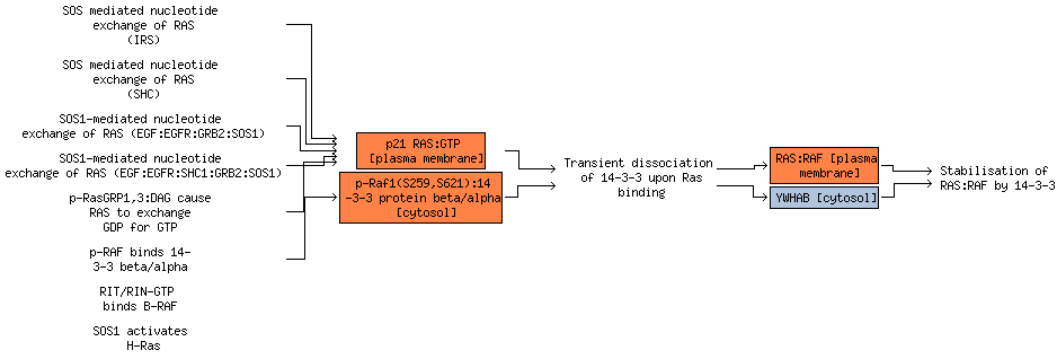
Inactive Raf-1 is associated in the cytoplasm with 14-3-3. 14-3-3 binds to Raf-1 via the Ser259 phosphorylation site (S1). This interaction stabilises the inactive conformation of Raf-1 in which the Ras-binding Cysteine-rich domain (CRD) is obscured. The Raf-1 molecule contains an additional p21ras-binding domain (RBD), a second serine phosphorylation site at S621 (S2) and two tyrosine phosphorylation sites (at 340, Y1 and 341, Y2).



References

Morrison DK, Cutler RE, "The complexity of Raf-1 regulation.", Curr Opin Cell Biol, 9, 1997, 174-9.

1.1.2 Transient dissociation of 14-3-3 upon Ras binding (Reaction)



Authors

Charalambous, M, 2005-01-07 11:17:43.

Editors

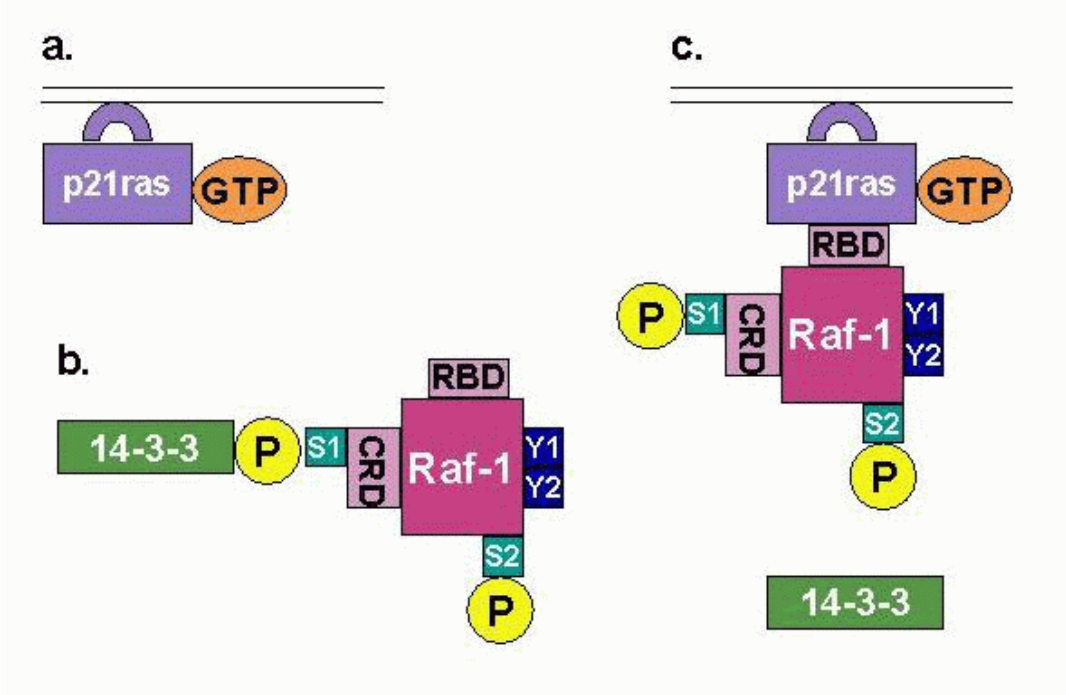
Schmidt, EE, 0000-00-00 00:00:00.

Reviewers

Heldin, CH, 2008-02-12 09:44:02.

Activated p21ras (the GTP-bound form) is associated with the plasma membrane. Inactive Raf-1 is associated in the cytoplasm with 14-3-3. 14-3-3 binds to Raf-1 via the Ser259 phosphorylation site (S1). This interaction stabilises the inactive conformation of Raf-1 in which the Ras-binding Cysteine-rich domain (CRD) is obscured. The Raf-1 molecule contains an additional p21ras-binding domain (RBD), a second serine phosphorylation site at S621 (S2) and two tyrosine phosphorylation sites (at 340, Y1 and 341, Y2).

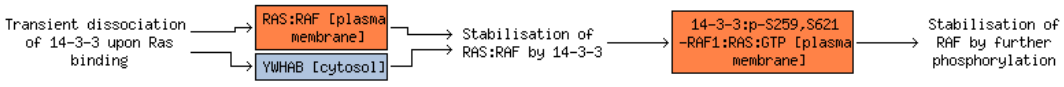
Raf-1 binds activated p21ras via the RBD. This displaces 14-3-3 from Ser259 and unmasks the CRD.



References

Morrison DK, Cutler RE, "The complexity of Raf-1 regulation.", Curr Opin Cell Biol, 9, 1997, 174-9.

1.1.3 Stabilisation of RAS:RAF by 14-3-3 (Reaction)



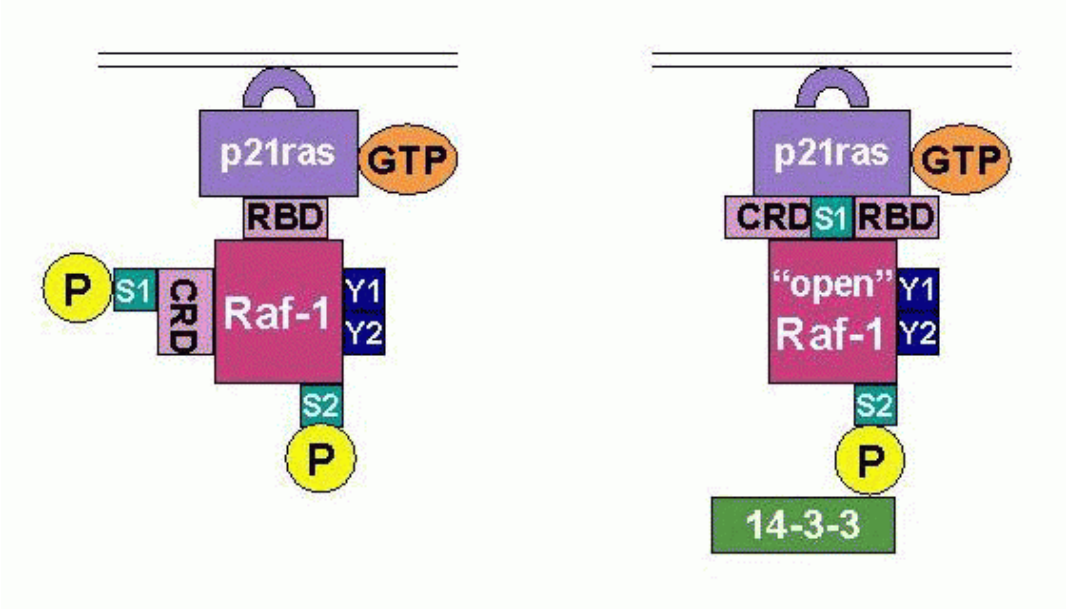
Authors

Charalambous, M, 2005-01-07 11:17:43.

Editors

Schmidt, EE, 0000-00-00 00:00:00.

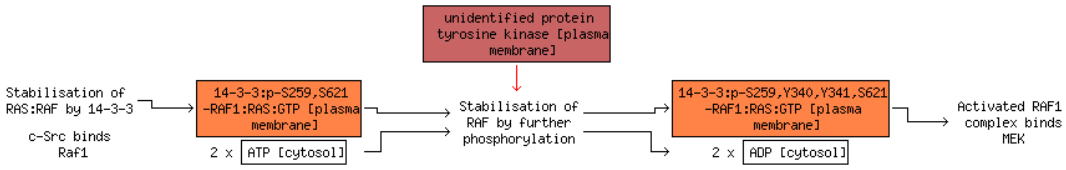
14-3-3 has been displaced from Ser259. 14-3-3 may now bind its higher affinity Ser621 (S2) site. This stabilises an 'open' Raf-1 conformation that is catalytically active, and bound to p21ras via both p21ras-binding domains, CRD and RBD.



References

Morrison DK, Cutler RE, "The complexity of Raf-1 regulation.", Curr Opin Cell Biol, 9, 1997, 174-9.

1.1.4 Stabilisation of RAF by further phosphorylation (Reaction)



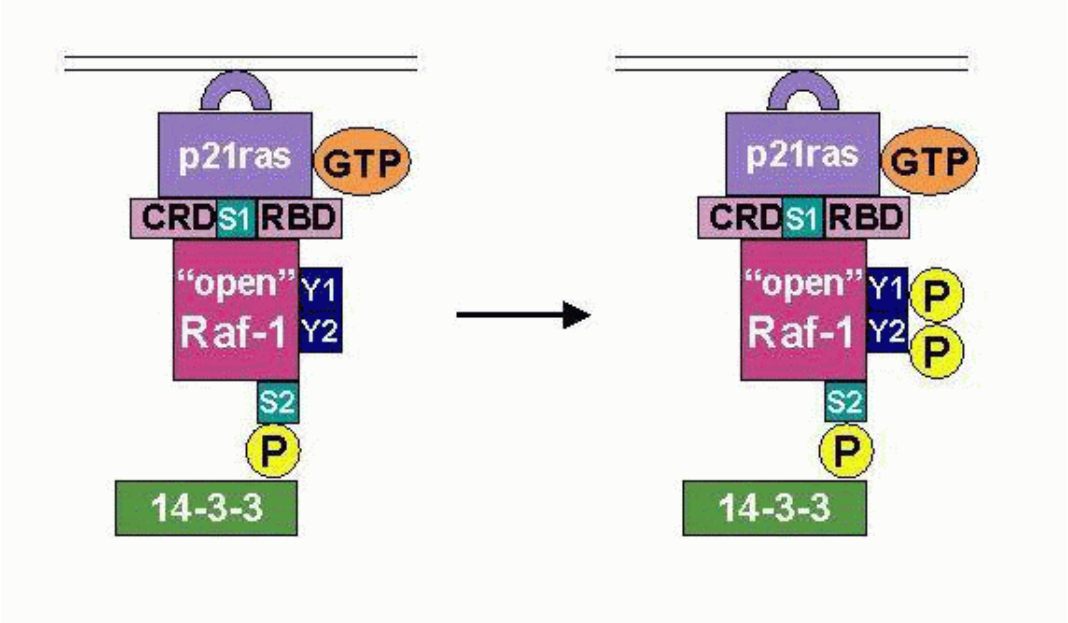
Authors

Charalambous, M, 2005-01-07 11:17:43.

Editors

Schmidt, EE, 0000-00-00 00:00:00.

An unidentified protein tyrosine kinase located in the plasma membrane phosphorylates tyrosine residues at 340 and 341 (Y1, Y2 in diagram) of Raf-1. This serves to further stabilise the active 'open' Raf-1 conformation. While the kinase has not been definitively identified, Src is a plausible candidate: coexpression of Raf-1 and Src in Sf9 cells resulted in phosphorylation of Y340/Y341 and enzymatic activationof Raf-1; Raf-1 interacts with Src and co-immunoprecipitates with Src/Fyn in NIH-3T3 cells.



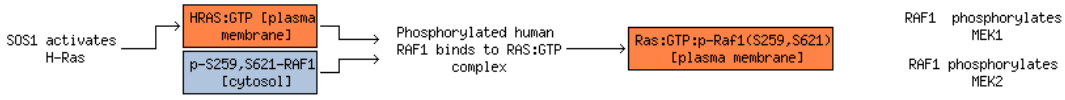
References

Cleghon V, Morrison DK, "Raf-1 interacts with Fyn and Src in a non-phosphotyrosine-dependent manner", J Biol Chem, 269, 1994, 17749-55.

Fabian JR, Daar IO, Morrison DK, "Critical tyrosine residues regulate the enzymatic and biological activity of Raf-1 kinase", Mol Cell Biol, 13, 1993, 7170-9.

Morrison DK, Cutler RE, "The complexity of Raf-1 regulation.", Curr Opin Cell Biol, 9, 1997, 174-9.

1.1.5 Phosphorylated human RAF1 binds to RAS:GTP complex (Reaction)



Authors

Williams, MG, 2007-10-30 11:44:05.

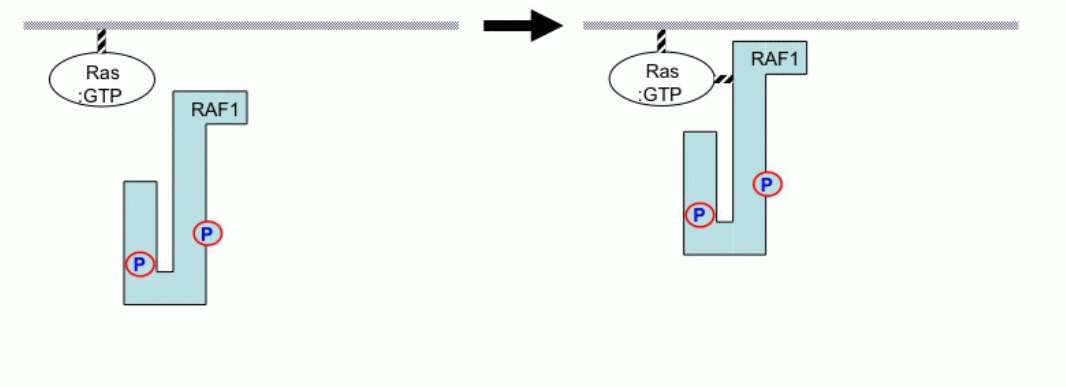
Editors

Jupe, S, 2010-08-06.

Reviewers

Villarino, A, 2011-02-11, Dooms, H, 2011-03-17.

A key event for Ras transformation involves the direct physical association between Ras and the Raf-1 kinase. This interaction promotes both Raf translocation to the plasma membrane and activation of Raf kinase activity.



References

Brtva TR, Drugan JK, Ghosh S, Terrell RS, Campbell-Burk S, Bell RM, Der CJ, "Two distinct Raf domains mediate interaction with Ras", J Biol Chem, 270, 1995, 9809-12.

Stokoe D, Macdonald SG, Cadwallader K, Symons M, Hancock JF, "Activation of Raf as a result of recruitment to the plasma membrane", Science, 264, 1994, 1463-7.

1.2 MEK activation (Pathway)

Authors

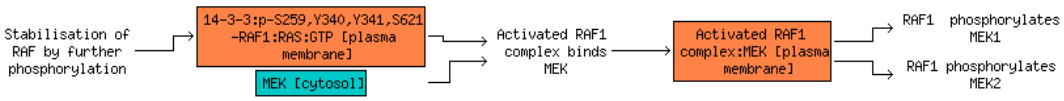
Charalambous, M, 2004-04-29 09:21:24.

Reviewers

Greene, LA, 2007-11-08 15:39:37.

MEK is phosphorylated and activated by RAF.

1.2.1 Activated RAF1 complex binds MEK (Reaction)



Authors

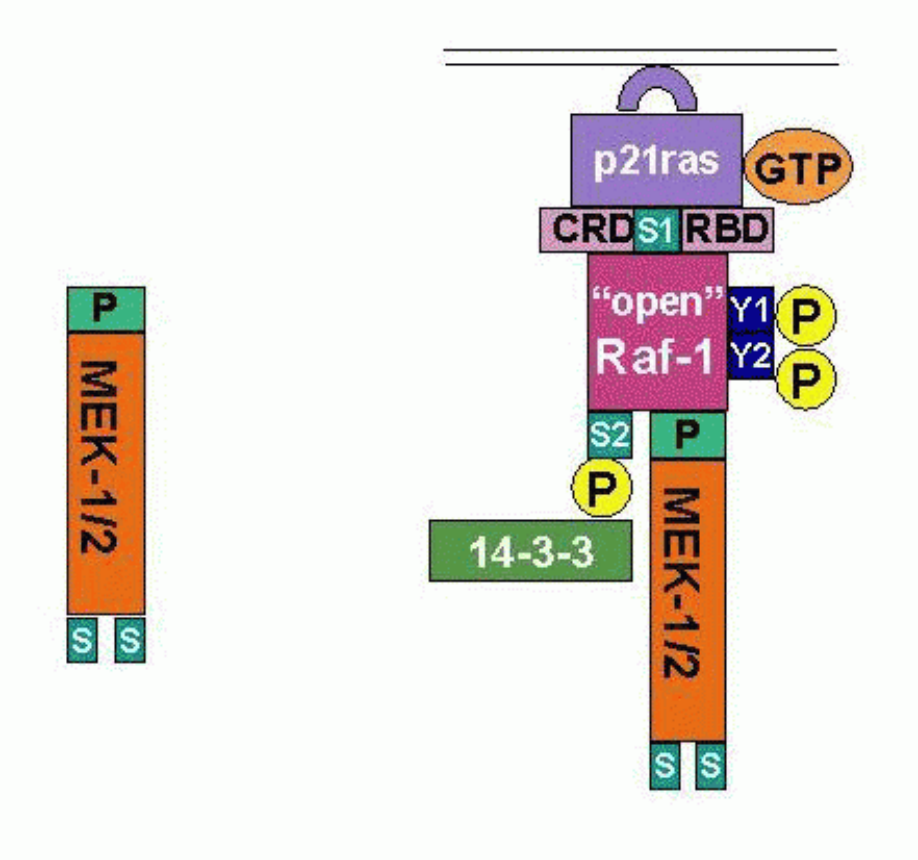
Charalambous, M, 2005-01-07 11:17:43.

Editors

Schmidt, EE, 0000-00-00 00:00:00.

MEK-1/2 have a proline rich domain (P) and critical Serine residues (MEK-1 S218/222, MEK-2 unknown, S) upon which the molecules may be phosphorylated. MEK1/2 are found in the cytoplasm of unstimulated cells.

MEK-1/2 bind to active Raf-1 via the proline-rich domain. Active Raf-1 is able to phosphorylate target Serine and Threonine residues in the presence of ATP.



Source reaction

This reaction was inferred from the corresponding reaction "Activated Raf complex binds MEK" in species Rattus norvegicus.

MEK-1/2 have a proline rich domain (P) and critical Serine residues (MEK-1 S218/222, MEK-2 unknown, S) upon which the molecules may be phosphorylated. MEK1/2 are found in the cytoplasm of unstimulated cells.

MEK-1/2 bind to active Raf-1 via the proline-rich domain. Active Raf-1 is able to phosphorylate target Serine and Threonine residues in the presence of ATP.

The following literature references support the source reaction:

Catling AD, Schaeffer HJ, Reuter CW, Reddy GR, Weber MJ, "A proline-rich sequence unique to MEK1 and MEK2 is required for raf binding and regulates MEK function.", Mol Cell Biol, 15, 1995, 5214-25.

1.2.2 RAF phosphorylates MEK (Pathway)

Authors

Charalambous, M, 2005-01-07 11:17:43.

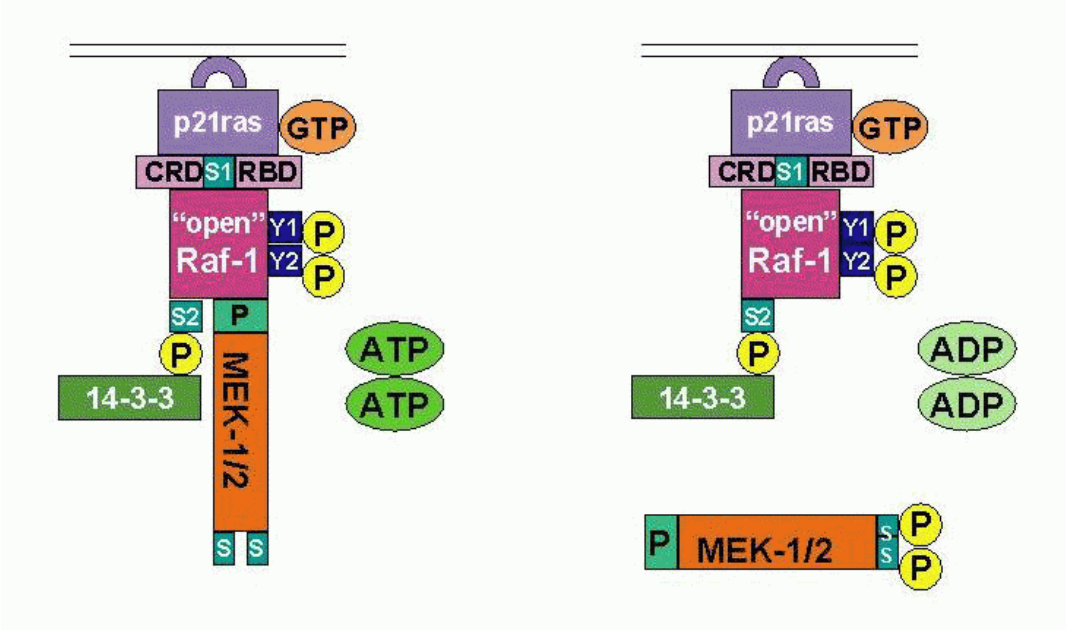
Editors

Schmidt, EE, 0000-00-00 00:00:00.

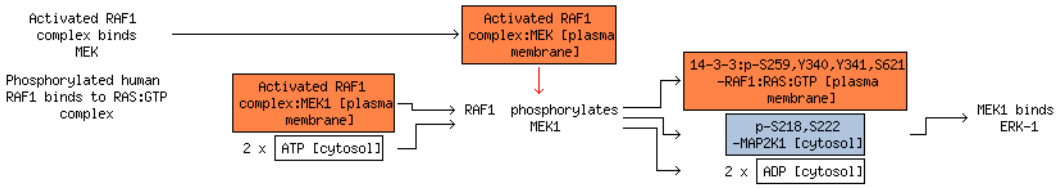
Reviewers

Villarino, A, 2011-02-11, Dooms, H, 2011-03-17.

Active Raf-1 phosphorylates MEK-1/2 on Serine residues, converting ATP to ADP. The MEK-1/2 kinase is now active.



1.2.2.1 RAF1 phosphorylates MEK1 (Reaction)



Authors

Charalambous, M, 2005-01-07 11:17:43.

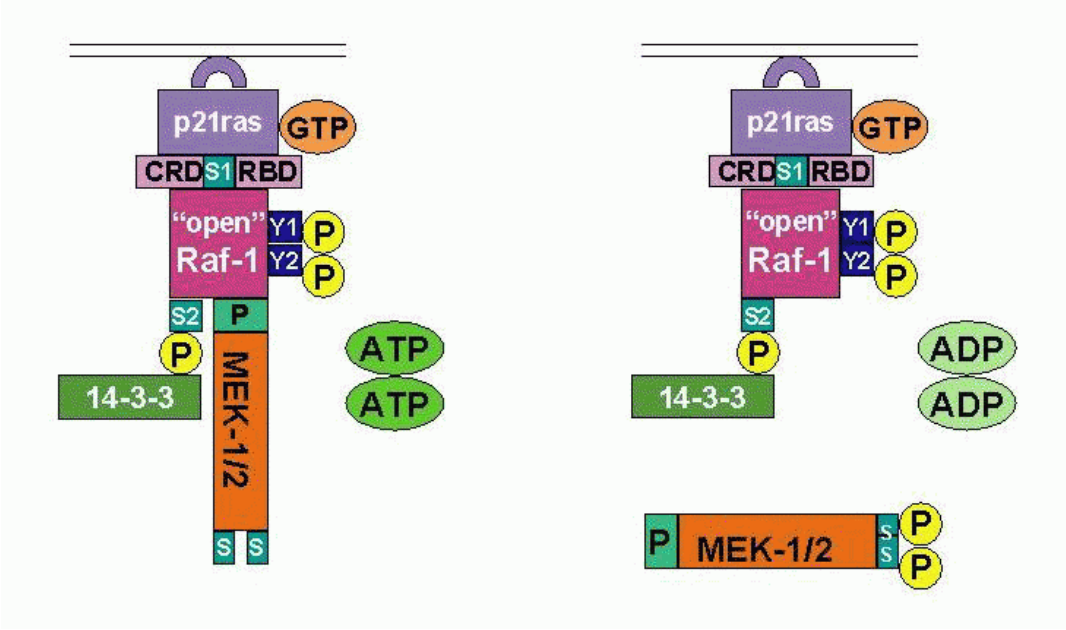
Editors

Schmidt, EE, 0000-00-00 00:00:00.

Reviewers

Villarino, A, 2011-02-11, Dooms, H, 2011-03-17.

Active Raf-1 phosphorylates MEK-1/2 on Serine residues, converting ATP to ADP. The MEK-1/2 kinase is now active.



Source reaction

This reaction was inferred from the corresponding reaction "Raf1 phosphorylates MEK1" in species Rattus norvegicus.

Active Raf-1 phosphorylates MEK-1/2 on Serine residues, converting ATP to ADP. The MEK-1/2 kinase is now active.

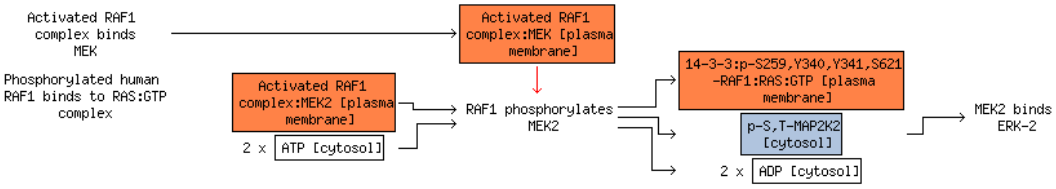
The following literature references support the source reaction:

Catling AD, Schaeffer HJ, Reuter CW, Reddy GR, Weber MJ, "A proline-rich sequence unique to MEK1 and MEK2 is required for raf binding and regulates MEK function.", Mol Cell Biol, 15, 1995, 5214-25.

Papin C, EychÃƒÂ¨ne A, Brunet A, PagÃƒÂ¨s G, PouyssÃ©gur J, Calothy G, Barnier JV, "B-Raf protein isoforms interact with and phosphorylate Mek-1 on serine residues 218 and 222.", Oncogene, 10, 1995, 1647-51.

Seger R, Seger D, Reszka AA, Munar ES, Eldar-Finkelman H, Dobrowolska G, Jensen AM, Campbell JS, Fischer EH, Krebs EG, "Overexpression of mitogen-activated protein kinase kinase (MAPKK) and its mutants in NIH 3T3 cells. Evidence that MAPKK involvement in cellular proliferation is regulated by phosphorylation of serine residues in its kinase subdomains VII and VIII.", J Biol Chem, 269, 1994, 25699-709.

1.2.2.2 RAF1 phosphorylates MEK2 (Reaction)



Authors

Charalambous, M, 2005-01-07 11:17:43.

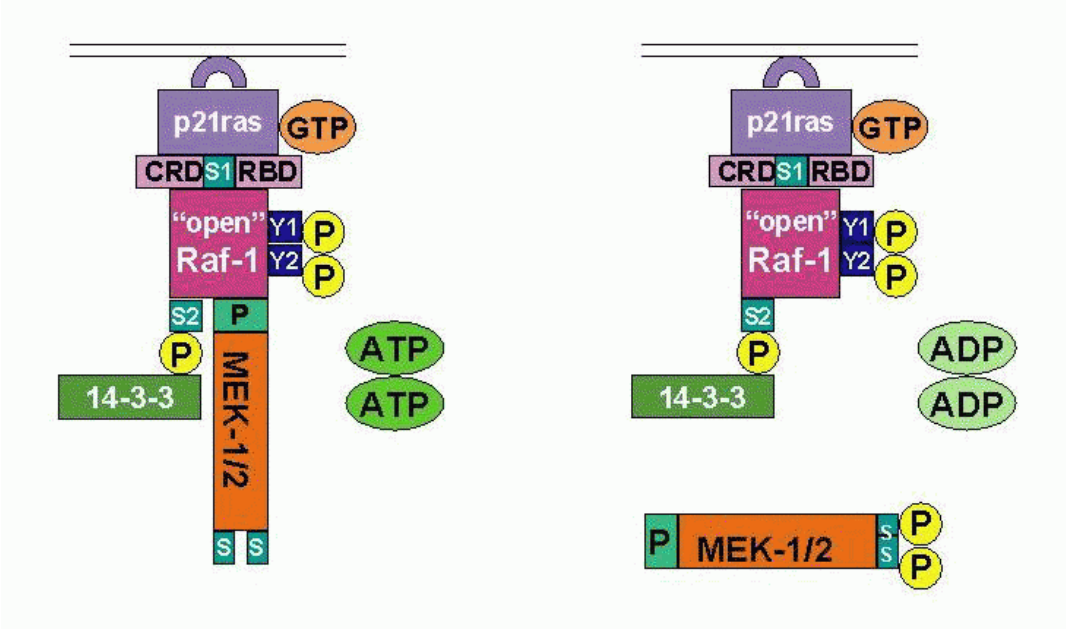
Editors

Schmidt, EE, 0000-00-00 00:00:00.

Reviewers

Villarino, A, 2011-02-11, Dooms, H, 2011-03-17.

Active Raf-1 phosphorylates MEK-1/2 on Serine residues, converting ATP to ADP. The MEK-1/2 kinase is now active.



Source reaction

This reaction was inferred from the corresponding reaction "Raf1 phosphorylates MEK2" in species Rattus norvegicus.

Active Raf-1 phosphorylates MEK-1/2 on Serine residues, converting ATP to ADP. The MEK-1/2 kinase is now active.

The following literature references support the source reaction:

Catling AD, Schaeffer HJ, Reuter CW, Reddy GR, Weber MJ, "A proline-rich sequence unique to MEK1 and MEK2 is required for raf binding and regulates MEK function.", Mol Cell Biol, 15, 1995, 5214-25.

1.3 ERK activation (Pathway)

Reviewers

Greene, LA, 2007-11-08 15:39:37.

Activated MEK phosphorylates and activates ERK.

1.3.1 ERK1 activation (Pathway)

Authors

Charalambous, M, 2005-02-04 06:50:22.

Editors

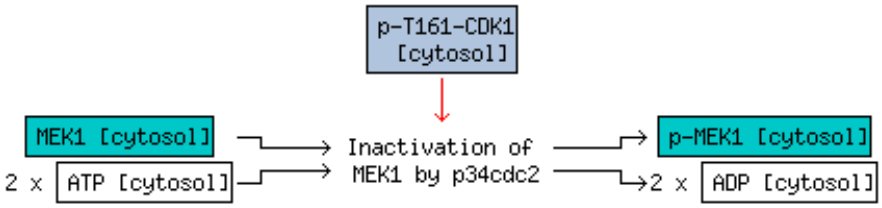
Schmidt, EE, 0000-00-00 00:00:00.

Reviewers

Greene, LA, 2007-11-08 15:39:37.

Activated MEK1 phosphorylates and activates ERK1.

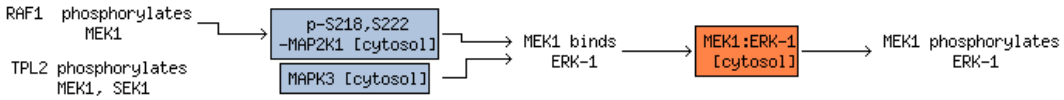
1.3.1.1 Inactivation of MEK1 by p34cdc2 (Reaction)



At the beginning of this reaction, 2 molecules of 'ATP', and 1 molecule of 'MEK1' are present. At the end of this reaction, 1 molecule of 'phospho_MEK1', and 2 molecules of 'ADP' are present.

This reaction takes place in the 'cytosol' and is mediated by the 'protein serine/threonine kinase activity' of 'phospho-Cdc2 (Thr 161)'.

1.3.1.2 MEK1 binds ERK-1 (Reaction)



Authors

Charalambous, M, 2005-02-04 06:50:22.

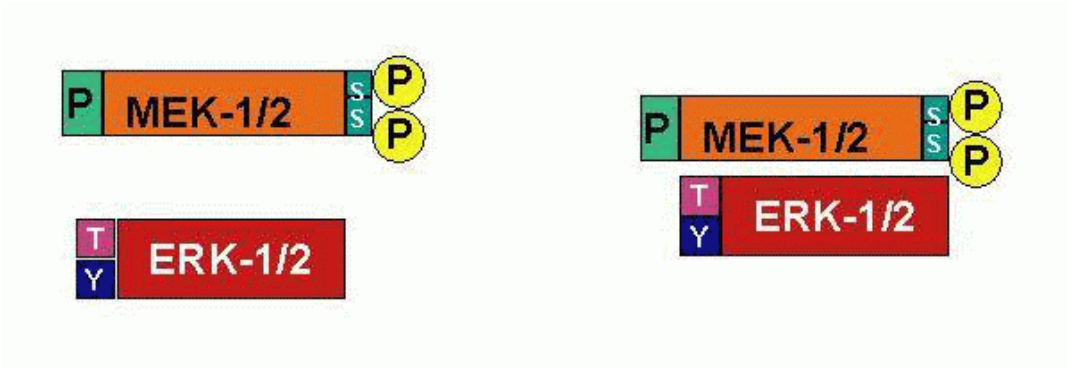
Editors

Schmidt, EE, 0000-00-00 00:00:00.

Reviewers

Greene, LA, 2007-11-08 15:39:37.

In the cytoplasm activated MEK1 (Serine phosphorylated) may encounter monomeric, inactive ERK1. ERK1 in its inactive form is not phosphorylated on a critical Threonine (T) and a critical Tyrosine (Y).



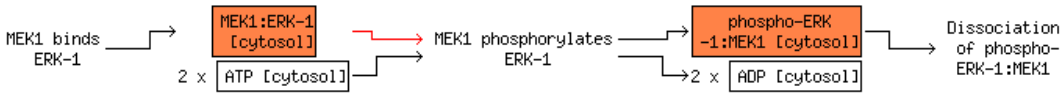
References

Zheng CF, Guan KL, "Cloning and characterization of two distinct human extracellular signal-regulated kinase activator kinases, MEK1 and MEK2.", J Biol Chem, 268, 1993, 11435-9.

Regulators of this Reaction

'IL6:Tyrosine phosphorylated hexameric IL-6 receptor:Activated JAKs:p-SHP2 [plasma membrane]' positively regulates 'MEK1 binds ERK-1' (references supporting this regulation: Dance M, Montagner A, Salles JP, Yart A, Raynal P, "The molecular functions of Shp2 in the Ras/Mitogen-activated protein kinase (ERK1/2) pathway", Cell Signal, 20, 2008, 453-9., Eulenfeld R, Schaper F, "A new mechanism for the regulation of Gab1 recruitment to the plasma membrane", J Cell Sci, 122, 2009, 55-64., Fukada T, Hibi M, Yamanaka Y, Takahashi-Tezuka M, Fujitani Y, Yamaguchi T, Nakajima K, Hirano T, "Two signals are necessary for cell proliferation induced by a cytokine receptor gp130: involvement of STAT3 in anti-apoptosis", Immunity, 5, 1996, 449-60., Kim H, Baumann H, "Dual signaling role of the protein tyrosine phosphatase SHP-2 in regulating expression of acute-phase plasma proteins by interleukin-6 cytokine receptors in hepatic cells", Mol Cell Biol, 19, 1999, 5326-38., Kim H, Hawley TS, Hawley RG, Baumann H, "Protein tyrosine phosphatase 2 (SHP-2) moderates signaling by gp130 but is not required for the induction of acute-phase plasma protein genes in hepatic cells", Mol Cell Biol, 18, 1998, 1525-33., Stahl N, Farruggella TJ, Boulton TG, Zhong Z, Darnell JE Jr, Yancopoulos GD, "Choice of STATs and other substrates specified by modular tyrosine-based motifs in cytokine receptors", Science, 267, 1995, 1349-53., Takahashi-Tezuka M, Yoshida Y, Fukada T, Ohtani T, Yamanaka Y, Nishida K, Nakajima K, Hibi M, Hirano T, "Gab1 acts as an adapter molecule linking the cytokine receptor gp130 to ERK mitogen-activated protein kinase", Mol Cell Biol, 18, 1998, 4109-17.)

1.3.1.3 MEK1 phosphorylates ERK-1 (Reaction)



Authors

Charalambous, M, 2005-02-04 06:50:22.

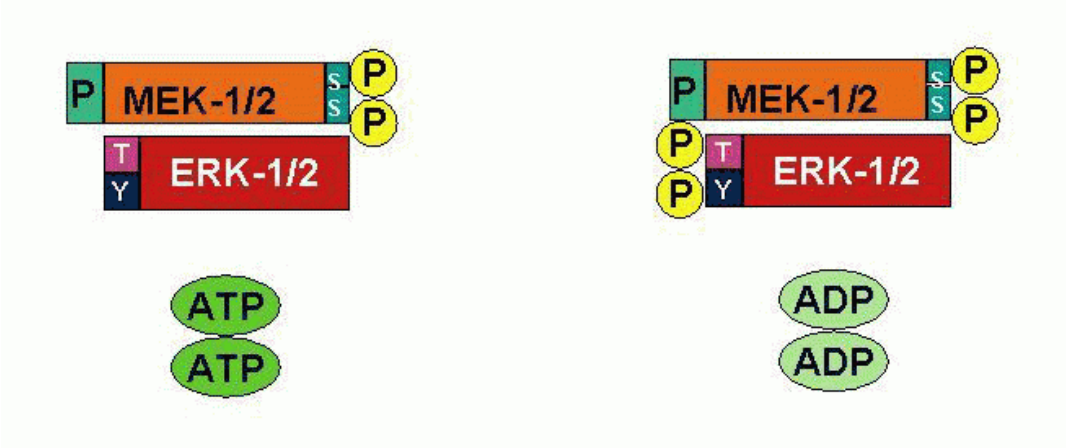
Editors

Schmidt, EE, 0000-00-00 00:00:00.

Reviewers

Greene, LA, 2007-11-08 15:39:37.

MEK1 phosphorylates the critical Tyrosine and Threonine on ERK1, converting two ATP to ADP. Phosphorylation of ERK-1 activates its kinase activity.



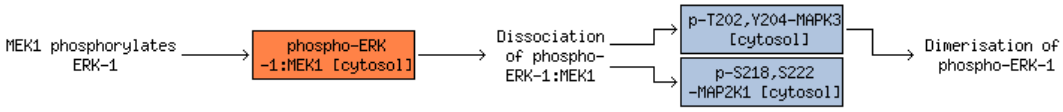
References

Zheng CF, Guan KL, "Cloning and characterization of two distinct human extracellular signal-regulated kinase activator kinases, MEK1 and MEK2.", J Biol Chem, 268, 1993, 11435-9.

Regulators of this Reaction

'p-MEK1 [cytosol]' negatively regulates 'MEK1 phosphorylates ERK-1'

1.3.1.4 Dissociation of phospho-ERK-1:MEK1 (Reaction)



Authors

Charalambous, M, 2005-02-04 06:50:22.

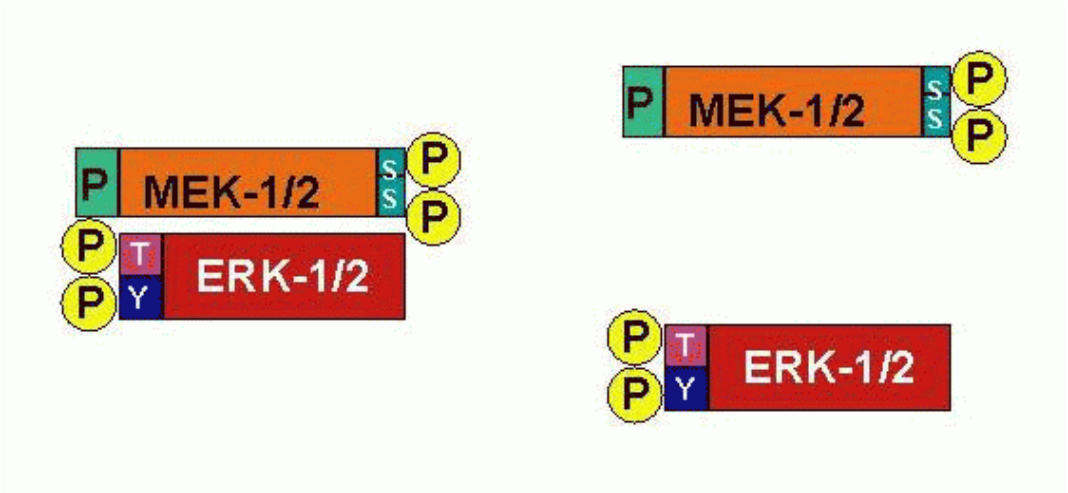
Editors

Schmidt, EE, 0000-00-00 00:00:00.

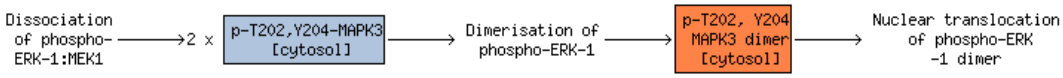
Reviewers

Gillespie, ME, 2010-11-24.

MEK1 dissociates from phospho-ERK1, allowing phospho-ERK1 to dimerise with another phospho-ERK1.



1.3.1.5 Dimerisation of phospho-ERK-1 (Reaction)



Authors

Charalambous, M, 2005-02-04 06:50:22.

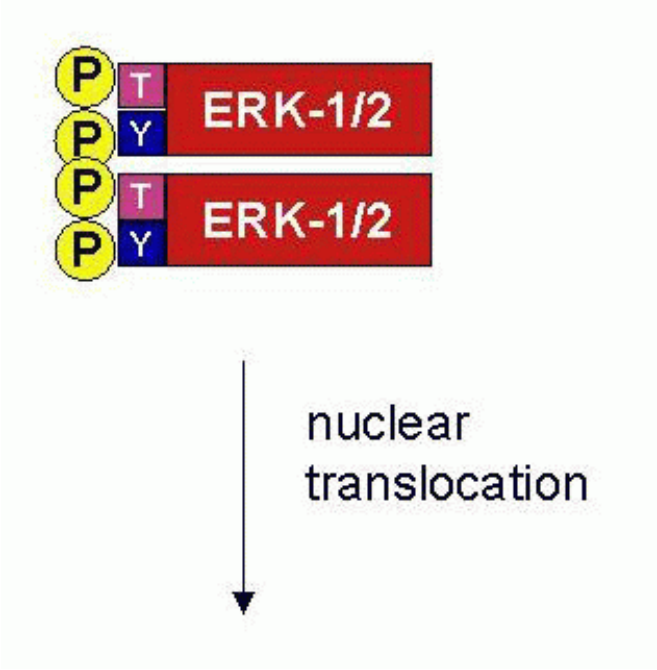
Editors

Schmidt, EE, 0000-00-00 00:00:00.

Reviewers

Greene, LA, 2007-11-08 15:39:37.

Two phospho-ERK1 molecules dimerise and enter the nucleus, where they may phosphorylate downstream targets.



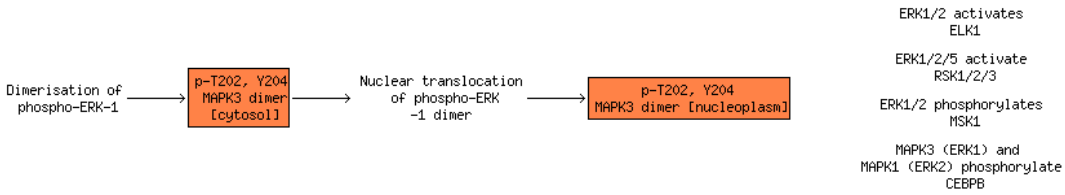
Source reaction

This reaction was inferred from the corresponding reaction "Dimerisation of phospho-ERK-2" in species Rattus norvegicus.

At the beginning of this reaction, 2 molecules of 'phospho-ERK2' is present. At the end of this reaction, 1 molecule of 'phospho-ERK2-dimer' is present.

This reaction takes place in the 'cytosol'.

1.3.1.6 Nuclear translocation of phospho-ERK-1 dimer (Reaction)



Authors

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Reviewers

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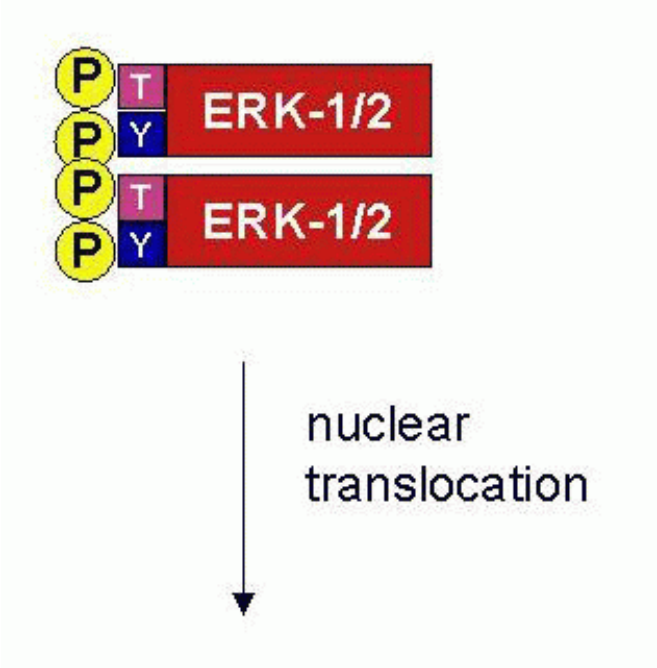
Phospho-ERK-1 dimer is translocated from cytosol to nucleoplasm.



Source reaction

This reaction was inferred from the corresponding reaction "Nuclear translocation of phospho-ERK-2 dimer" in species Rattus norvegicus.

In this reaction, 1 molecule of 'phospho-ERK2-dimer' is translocated from cytosol to nucleoplasm.

This reaction takes place in the 'intracellular'.

1.3.2 ERK2 activation (Pathway)

Authors

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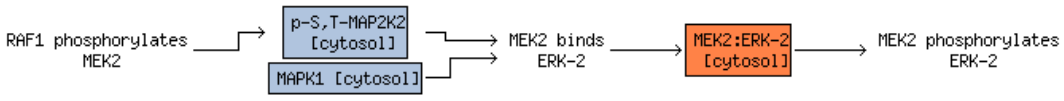
Activated MEK2 phosphorylates and activates ERK2.

1.3.2.1 MEK2 binds ERK-2 (Reaction)



Authors

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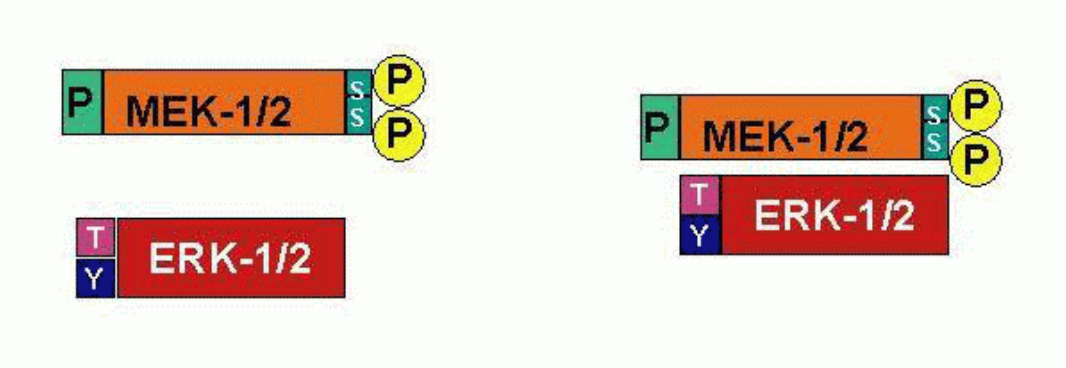
In the cytoplasm activated MEK2 (Serine phosphorylated) may encounter monomeric, inactive ERK2. ERK2 in its inactive form is not phosphorylated on a critical Threonine (T183) and a critical Tyrosine (Y185).



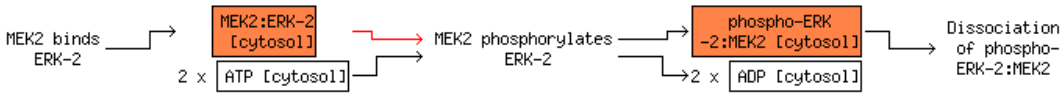
References

Zheng CF, Guan KL, "Cloning and characterization of two distinct human extracellular signal-regulated kinase activator kinases, MEK1 and MEK2.", J Biol Chem, 268, 1993, 11435-9.

Regulators of this Reaction

'IL6:Tyrosine phosphorylated hexameric IL-6 receptor:Activated JAKs:p-SHP2 [plasma membrane]' positively regulates 'MEK2 binds ERK-2' (references supporting this regulation: Dance M, Montagner A, Salles JP, Yart A, Raynal P, "The molecular functions of Shp2 in the Ras/Mitogen-activated protein kinase (ERK1/2) pathway", Cell Signal, 20, 2008, 453-9., Eulenfeld R, Schaper F, "A new mechanism for the regulation of Gab1 recruitment to the plasma membrane", J Cell Sci, 122, 2009, 55-64., Fukada T, Hibi M, Yamanaka Y, Takahashi-Tezuka M, Fujitani Y, Yamaguchi T, Nakajima K, Hirano T, "Two signals are necessary for cell proliferation induced by a cytokine receptor gp130: involvement of STAT3 in anti-apoptosis", Immunity, 5, 1996, 449-60., Kim H, Baumann H, "Dual signaling role of the protein tyrosine phosphatase SHP-2 in regulating expression of acute-phase plasma proteins by interleukin-6 cytokine receptors in hepatic cells", Mol Cell Biol, 19, 1999, 5326-38., Kim H, Hawley TS, Hawley RG, Baumann H, "Protein tyrosine phosphatase 2 (SHP-2) moderates signaling by gp130 but is not required for the induction of acute-phase plasma protein genes in hepatic cells", Mol Cell Biol, 18, 1998, 1525-33., Stahl N, Farruggella TJ, Boulton TG, Zhong Z, Darnell JE Jr, Yancopoulos GD, "Choice of STATs and other substrates specified by modular tyrosine-based motifs in cytokine receptors", Science, 267, 1995, 1349-53., Takahashi-Tezuka M, Yoshida Y, Fukada T, Ohtani T, Yamanaka Y, Nishida K, Nakajima K, Hibi M, Hirano T, "Gab1 acts as an adapter molecule linking the cytokine receptor gp130 to ERK mitogen-activated protein kinase", Mol Cell Biol, 18, 1998, 4109-17.)

1.3.2.2 MEK2 phosphorylates ERK-2 (Reaction)



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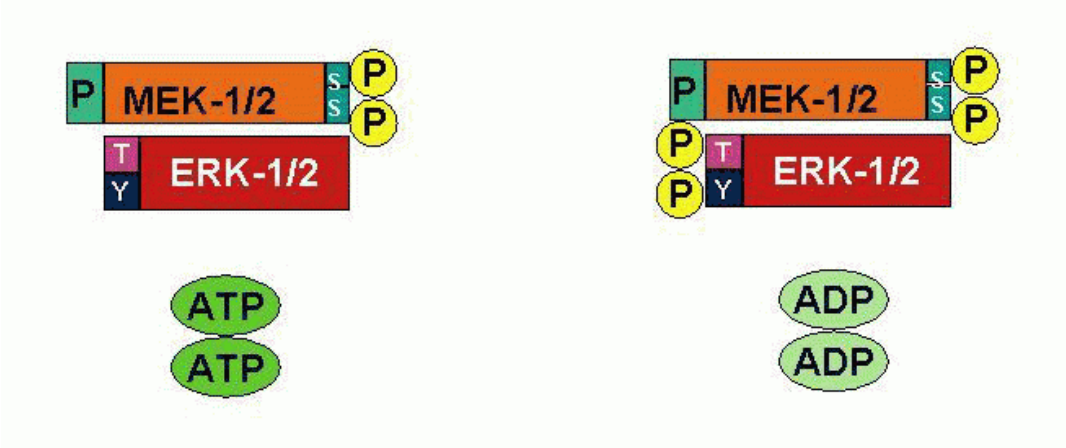
Reviewers

Greene, LA, 2007-11-08 15:39:37.

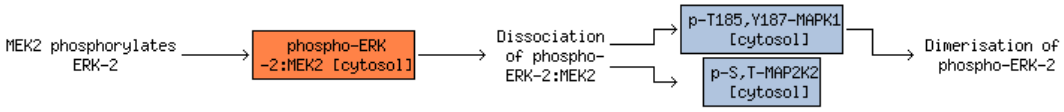
MEK2 phosphorylates the critical Tyrosine and Threonine on ERK2, converting two ATP to ADP. Phosphorylation of ERK-2 activates its kinase activity.



References

Zheng CF, Guan KL, "Cloning and characterization of two distinct human extracellular signal-regulated kinase activator kinases, MEK1 and MEK2.", J Biol Chem, 268, 1993, 11435-9.

1.3.2.3 Dissociation of phospho-ERK-2:MEK2 (Reaction)



Authors

Charalambous, M, 2005-02-04 06:50:22.

Editors

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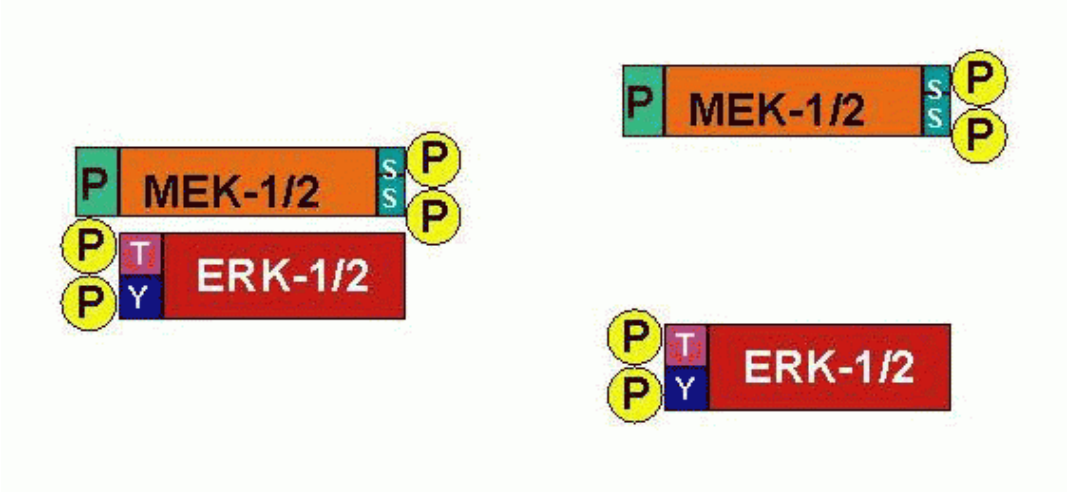
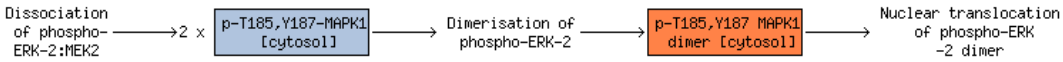
Reviewers

Gillespie, ME, 2010-11-24.

MEK2 dissociates from phospho-ERK2, allowing phospho-ERK2 to dimerise with another phospho-ERK2.



1.3.2.4 Dimerisation of phospho-ERK-2 (Reaction)



Authors

Charalambous, M, 2005-02-04 06:50:22.

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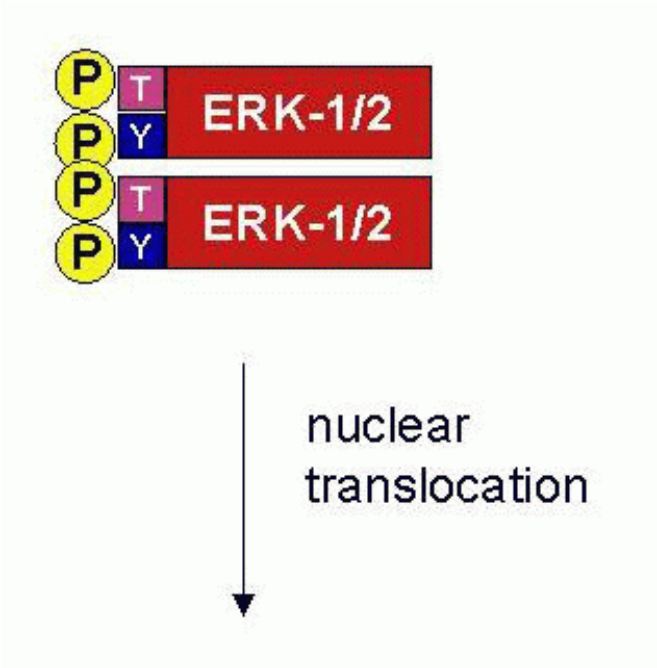
Two phospho-ERK2 molecules dimerise and enter the nucleus, where they may phosphorylate downstream targets.



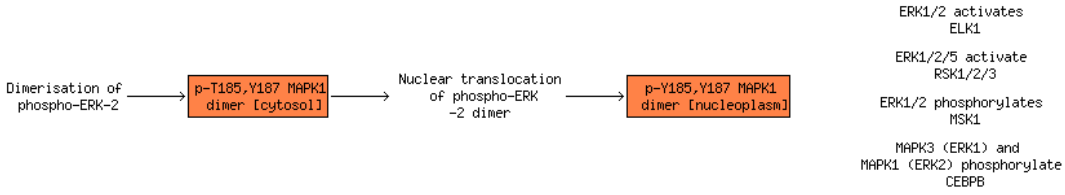
Source reaction

This reaction was inferred from the corresponding reaction "Dimerisation of phospho-ERK-2" in species Rattus norvegicus.

At the beginning of this reaction, 2 molecules of 'phospho-ERK2' is present. At the end of this reaction, 1 molecule of 'phospho-ERK2-dimer' is present.

This reaction takes place in the 'cytosol'.

1.3.2.5 Nuclear translocation of phospho-ERK-2 dimer (Reaction)



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Reviewers

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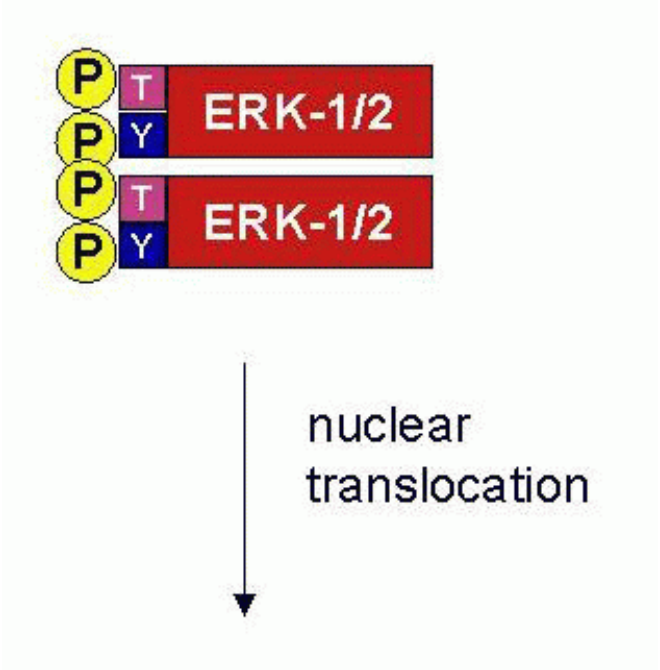
Phospho-ERK-2 dimer is translocated from cytosol to nucleoplasm.



Source reaction

This reaction was inferred from the corresponding reaction "Nuclear translocation of phospho-ERK-2 dimer" in species Rattus norvegicus.

In this reaction, 1 molecule of 'phospho-ERK2-dimer' is translocated from cytosol to nucleoplasm.

This reaction takes place in the 'intracellular'.

Full List of Literature References for Pathway "RAF/MAP kinase cascade"

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