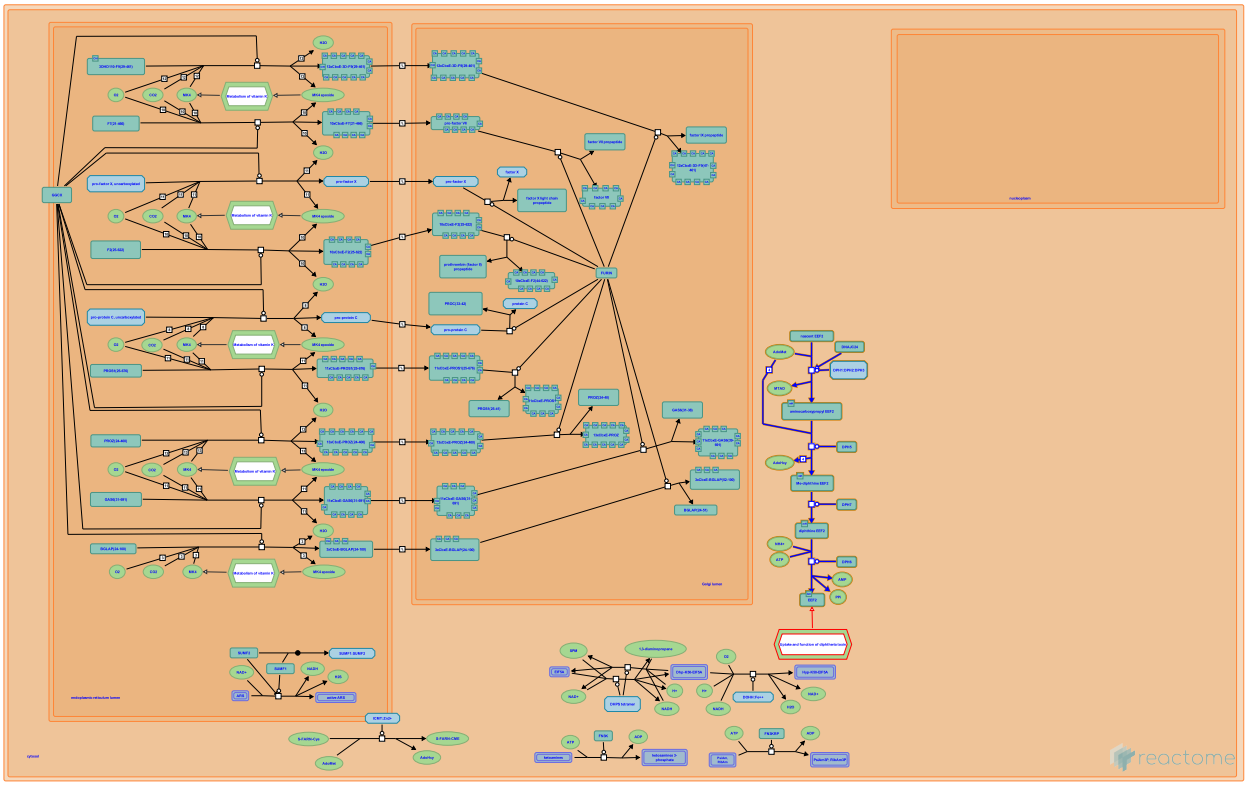
Synthesis of diphthamide-EEF2



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25/06/2019

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.

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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. ↗

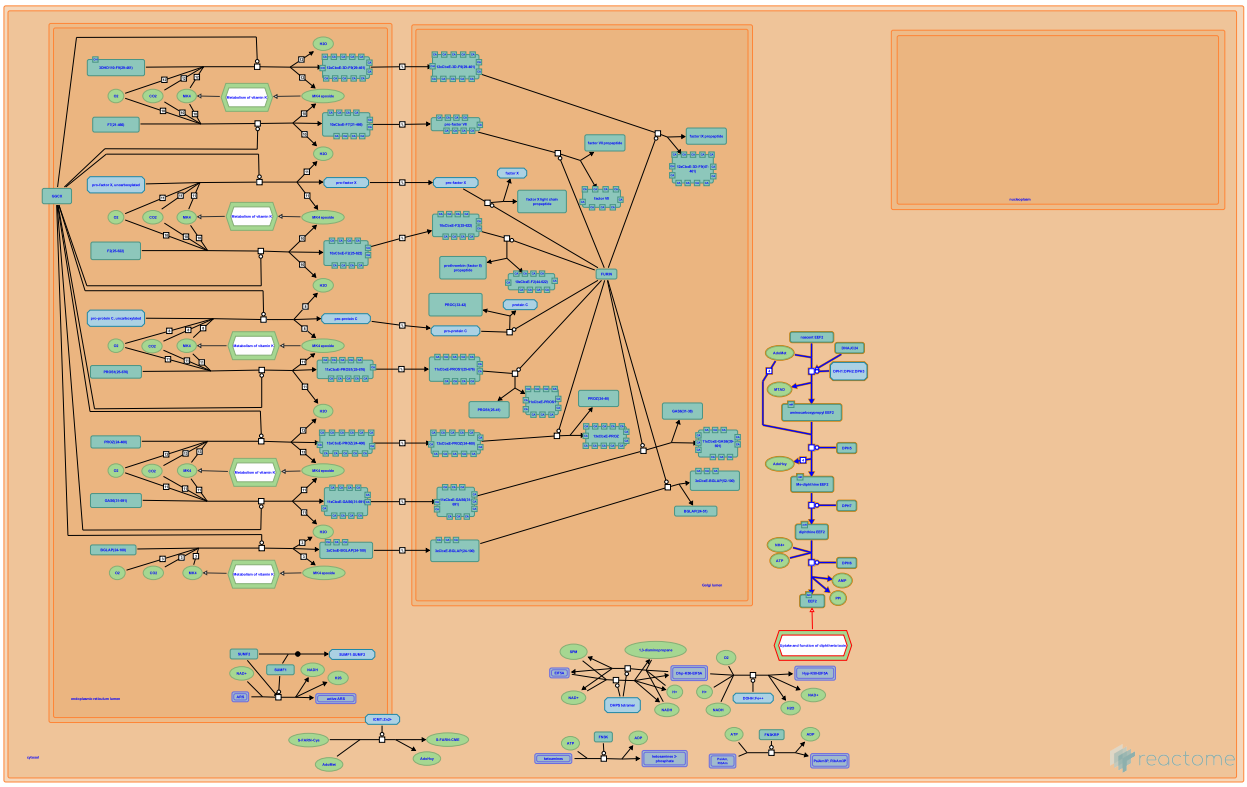
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Synthesis of diphthamide-EEF2 ↗

Stable identifier: R-HSA-5358493

Compartments: cytosol



Eukaryotic elongation factor 2 (EEF2) catalyzes the GTP dependent ribosomal translocation step during translation elongation. This function requires the presence of a posttranslational modification, the conversion of histidine residue 715 to diphthamide (2' [3 carboxamido 3 (trimethylammonio)propyl] L histidine) (Van Ness et al. 1978). No other protein is known to undergo this modification. The diphthamide residue is also the target of ADP ribosylation catalyzed by diphtheria toxin, which inactivates EEF2 and leads to cell death (Collier 1975; Pappenheim 1977).

Diphthamide synthesis proceeds in four steps: the transfer of 3 amino 3 carboxypropyl group from S adenosylmethionine to histidine 715 of EEF2, the addition of four methyl groups to the 3 amino 3 carboxypropyl moiety, the demethylation of the methylated carboxylate group to form diphthine, and the amidation of the diphthine carboxyl group (Liu et al. 2004; Lin et al. 2014; Schaffrath et al. 2014; Su et al. 2013; Uthman et al. 2013).

Literature references

Collier, RJ. (1975). Diphtheria toxin: mode of action and structure. *Bacteriol Rev, 39*, 54-85. ↗

Liu, S., Milne, GT., Kuremsky, JG., Fink, GR., Leppla, SH. (2004). Identification of the proteins required for biosynthesis of diphthamide, the target of bacterial ADP-ribosylating toxins on translation elongation factor 2. *Mol. Cell. Biol., 24*, 9487-97. ↗

Pappenheimer, AM. (1977). Diphtheria toxin. *Annu. Rev. Biochem., 46*, 69-94. ↗

Lin, Z., Su, X., Chen, W., Ci, B., Zhang, S., Lin, H. (2014). Dph7 catalyzes a previously unknown demethylation step in diphthamide biosynthesis. *J. Am. Chem. Soc.*. ↗

Su, X., Lin, Z., Lin, H. (2013). The biosynthesis and biological function of diphthamide. *Crit. Rev. Biochem. Mol. Biol., 48*, 515-21. ↗

Editions

2014-03-29	Authored, Edited	D'Eustachio, P.
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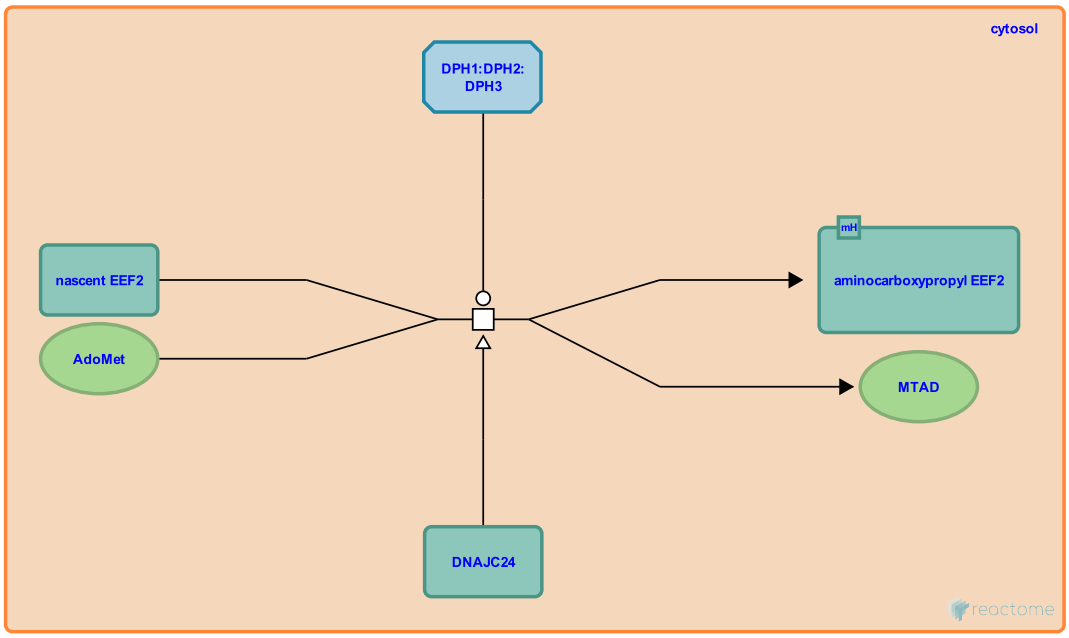
DPH2 transfers a 3-amino-3-carboxypropyl group from AdoMet to residue 715 of nascent EEF2 ↗

Location: Synthesis of diphthamide-EEF2

Stable identifier: R-HSA-5358494

Type: transition

Compartments: cytosol



The diphthamide biosynthesis protein 2 (DPH2) subunit of the cytosolic DPH1:DPH2:DPH3 complex catalyzes the transfer of a 3-amino-3-carboxypropyl group from S-adenosylmethionine (AdoMet) to residue 715 of nascent elongation factor 2 (EEF2), forming aminocarboxypropyl EEF2 and S-methylthioadenosine (MTAD). The association of DPH1, 2, and 3 to form a complex is inferred from studies of the homologous yeast proteins (Abdel-Fattah et al. 2013; Bar et al. 2008) and more limited studies of interactions among mouse and human ones (Liu et al. 2004). The identification of DPH2 as the catalytically active subunit of the DPH1:DPH2:DPH3 complex is inferred from the properties of the homologous Pyrococcus horikoshii protein (Zhang et al. 2010). DPH4 (DNAJC24) is needed for the reaction to occur but its exact role is unknown (Liu et al. 2004; Su et al. 2013). DPH3 is an electron donor for DPH1-DPH2 in the first step of diphthamide biosynthesis (Dong et al. 2014).

Followed by: DPH5 transfers four methyl groups from AdoMet to aminocarboxypropyl EEF2

Literature references

Abdel-Fattah, W., Scheidt, V., Uthman, S., Stark, MJ., Schaffrath, R. (2013). Insights into diphthamide, key diphtheria toxin effector. *Toxins (Basel), 5*, 958-68. ↗

Bär, C., Zabel, R., Liu, S., Stark, MJ., Schaffrath, R. (2008). A versatile partner of eukaryotic protein complexes that is involved in multiple biological processes: Kti11/Dph3. *Mol. Microbiol., 69*, 1221-33. ↗

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Su, X., Lin, Z., Lin, H. (2013). The biosynthesis and biological function of diphthamide. *Crit. Rev. Biochem. Mol. Biol., 48*, 515-21. ↗

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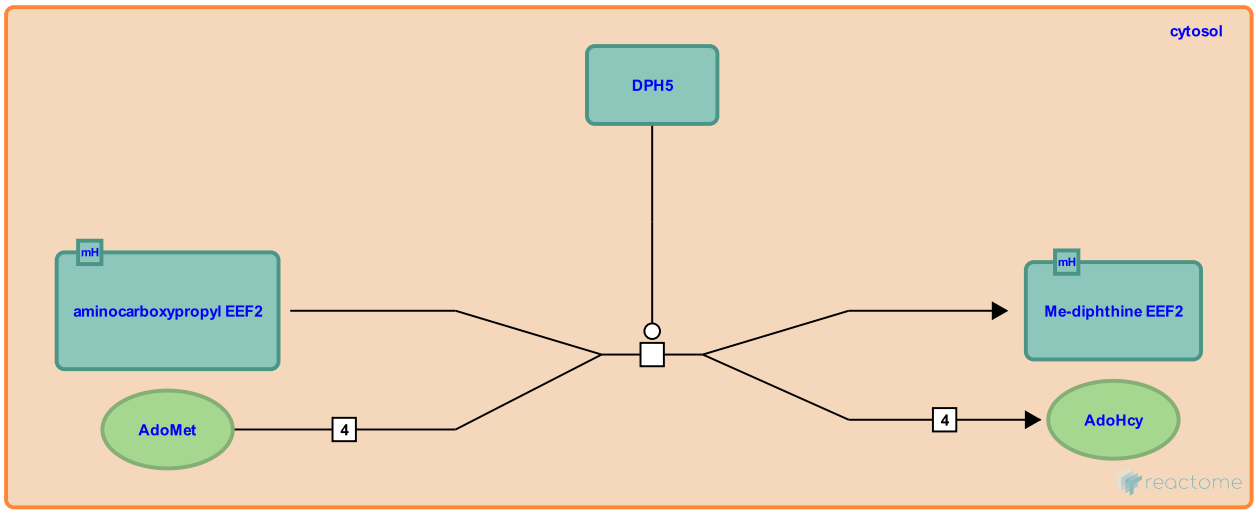
DPH5 transfers four methyl groups from AdoMet to aminocarboxypropyl EEF2 ↗

Location: Synthesis of diphthamide-EEF2

Stable identifier: R-HSA-5358484

Type: transition

Compartments: cytosol



Cytosolic diphthamide biosynthesis protein 5 (DPH5) transfers four methyl groups from S-adenosylmethionine (AdoMet) to elongation factor 2 (EEF2) whose histidine residue at position 715 has been conjugated with a 3-amino 3-carboxypropyl group, forming methylated diphthine EEF2 and S-adenosylhomocysteine (AdoHcy). DPH5 activity has been identified in cells of diverse eukaryotic species including humans and has been characterized in detail in budding yeast (Liu et al. 2004; Matteakis et al. 1992; Moehring & Moehring 1988).

Preceded by: DPH2 transfers a 3-amino-3-carboxypropyl group from AdoMet to residue 715 of nascent EEF2

Followed by: DPH7 hydrolyzes a methyl group on Me-diphthine EEF2

Literature references

Liu, S., Milne, GT., Kuremsky, JG., Fink, GR., Leppla, SH. (2004). Identification of the proteins required for biosynthesis of diphthamide, the target of bacterial ADP-ribosylating toxins on translation elongation factor 2. *Mol. Cell. Biol., 24*, 9487-97. ↗

Mattheakis, LC., Shen, WH., Collier, RJ. (1992). DPH5, a methyltransferase gene required for diphthamide biosynthesis in Saccharomyces cerevisiae. *Mol. Cell. Biol., 12*, 4026-37. ↗

Moehring, JM., Moehring, TJ. (1988). The post-translational trimethylation of diphthamide studied in vitro. *J. Biol. Chem., 263*, 3840-4. ↗

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DPH7 hydrolyzes a methyl group on Me-diphthine EEF2 ↗

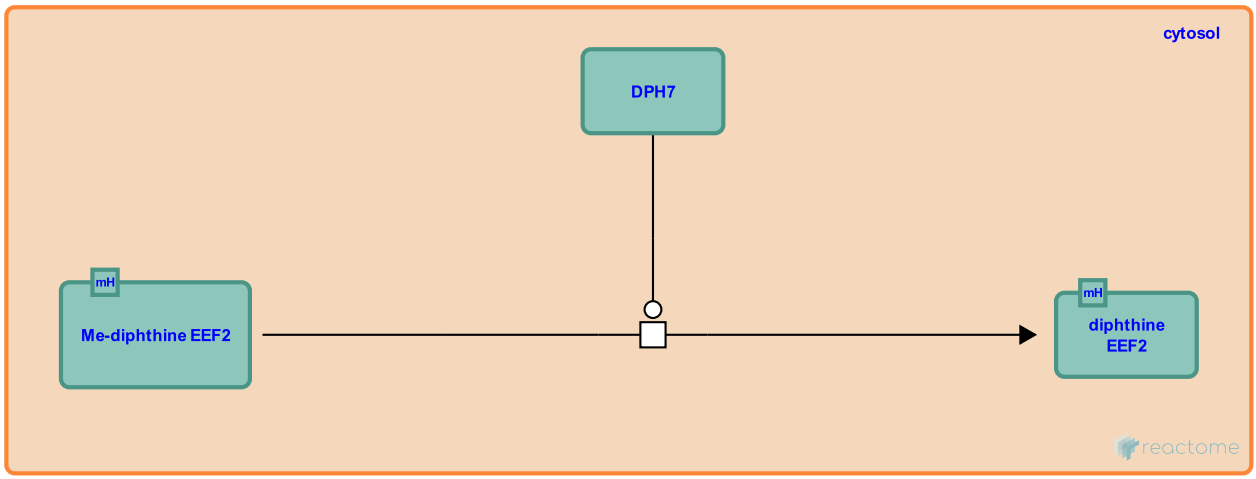
Location: Synthesis of diphthamide-EEF2

Stable identifier: R-HSA-5367022

Type: transition

Compartments: cytosol

Inferred from: Diphthamide biosynthesis protein 7 hydrolyzes a methyl group on Me-diphthine elongation factor 2 (Saccharomyces cerevisiae)



By analogy to the activity of its experimentally characterized budding yeast homolog (Lin et al. 2014; Schaffrath et al. 2014), cytosolic DPH7 is inferred to catalyze the removal of a methyl group of Me-diphthine EEF2, yielding diphthine EEF2.

Preceded by: DPH5 transfers four methyl groups from AdoMet to aminocarboxypropyl EEF2

Followed by: DPH6 ligates ammonium to diphthine-EEF2

Literature references

Lin, Z., Su, X., Chen, W., Ci, B., Zhang, S., Lin, H. (2014). Dph7 catalyzes a previously unknown demethylation step in diphthamide biosynthesis. *J. Am. Chem. Soc.*. ↗

Schaffrath, R., Abdel-Fattah Mohamed, W., Klassen, R., Stark, MJ. (2014). The Diphthamide Modification Pathway from Saccharomyces cerevisiae - Revisited. *Mol. Microbiol.*. ↗

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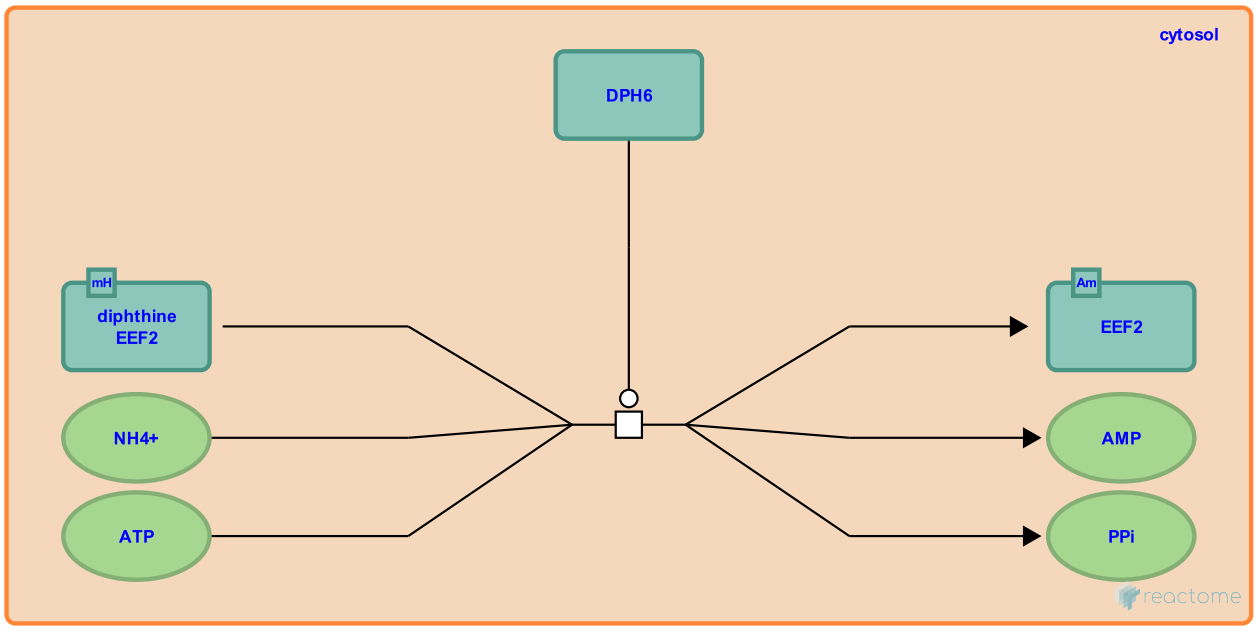
DPH6 ligates ammonium to diphthine-EEF2 ↗

Location: Synthesis of diphthamide-EEF2

Stable identifier: R-HSA-5358475

Type: transition

Compartments: cytosol



Cytosolic diphthamide biosynthesis protein 6 (DPH6) ligates an ammonium ion to diphthine-EEF2 to generate diphthamide-EEF2 in a reaction coupled to the hydrolysis of ATP to yield AMP and PPi (Su et al. 2012; Uthman et al. 2013; Wei et al. 2013).

Preceded by: DPH7 hydrolyzes a methyl group on Me-diphthine EEF2

Literature references

Su, X., Lin, Z., Chen, W., Jiang, H., Zhang, S., Lin, H. (2012). Chemogenomic approach identified yeast YLR143W as diphthamide synthetase. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19983-7. ↗

Uthman, S., Bär, C., Scheidt, V., Liu, S., ten Have, S., Giorgini, F. et al. (2013). The amidation step of diphthamide biosynthesis in yeast requires DPH6, a gene identified through mining the DPH1-DPH5 interaction network. *PLoS Genet., 9*, e1003334. ↗

Wei, H., Bera, TK., Wayne, AS., Xiang, L., Colantonio, S., Chertov, O. et al. (2013). A modified form of diphthamide causes immunotoxin resistance in a lymphoma cell line with a deletion of the WDR85 gene. *J. Biol. Chem., 288*, 12305-12. ↗

Editions

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