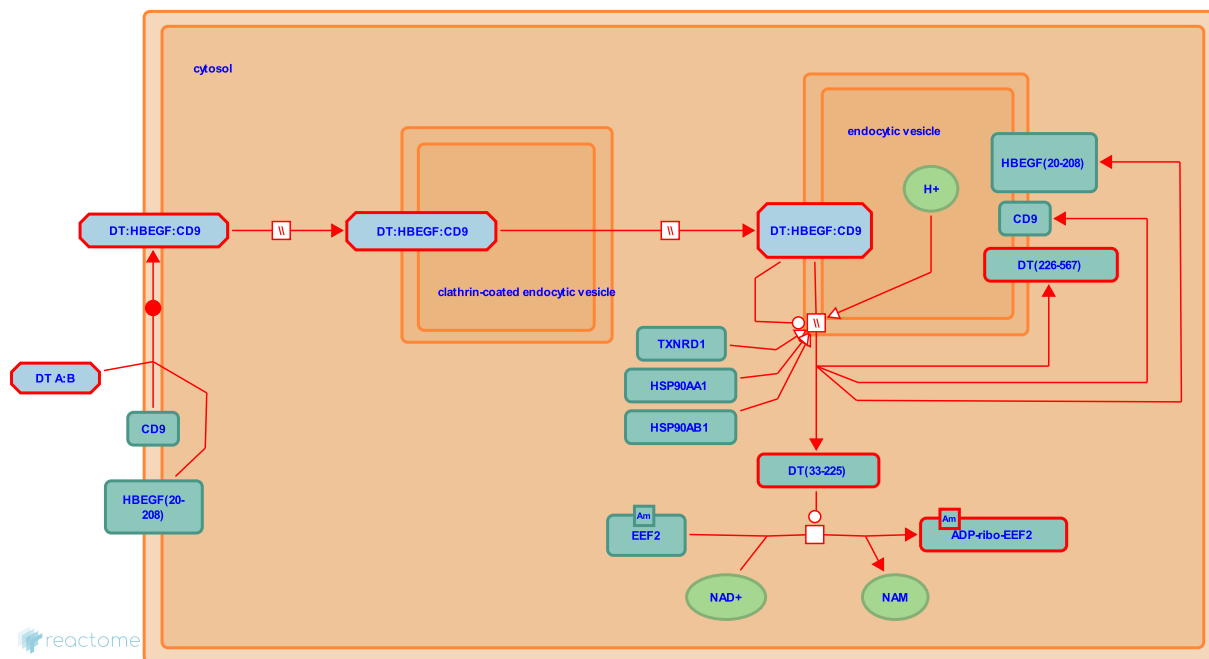


Uptake and function of diphtheria toxin



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook).

09/04/2024

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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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. [↗](#)

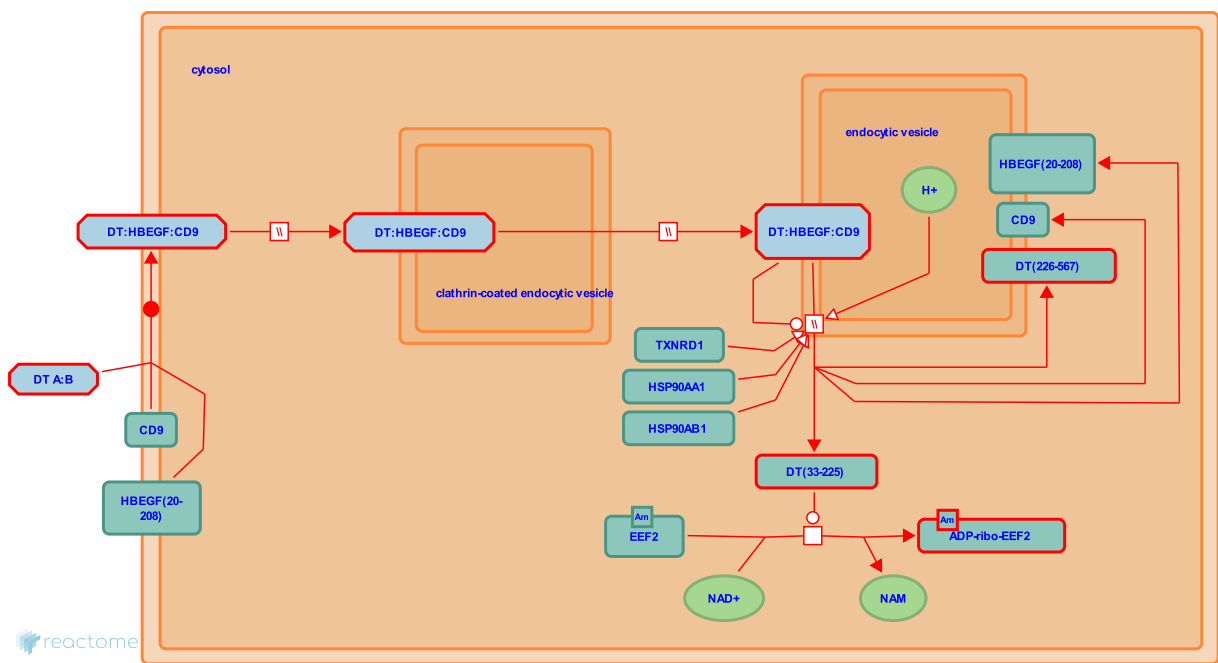
Reactome database release: 88

This document contains 1 pathway and 5 reactions ([see Table of Contents](#))

Uptake and function of diphtheria toxin [↗](#)

Stable identifier: R-HSA-5336415

Diseases: diphtheria



Diphtheria is a serious, often fatal human disease associated with damage to many tissues. Bacteria in infected individuals, however, are typically confined to the lining of the throat or to a skin lesion; systemic effects are due to the secretion of an exotoxin encoded by a lysogenic bacteriophage. The toxin is encoded as a single polypeptide but is cleaved by host furin-like proteases to yield an aminoterminal fragment A and a carboxyterminal fragment B, linked by a disulfide bond. Toxin cleavage can occur when it first contacts the target cell surface, as annotated here, or as late as the point at which fragment A is released into the cytosol. Fragment B mediates toxin uptake into target cell endocytic vesicles, where acidification promotes a conformational change enabling fragment B to form a channel in the vesicle membrane through which fragment A is extruded into the target cell cytosol. Cleavage of the inter-fragment disulfide bond frees DT fragment A, which catalyzes ADP ribosylation of the translation elongation factor 2 (EEF2) in a target cell, thereby blocking protein synthesis. Neither fragment is toxic to human cells by itself (Collier 1975; Pappenheim 1977; Murphy 2011).

Literature references

Murphy, JR. (2011). Mechanism of diphtheria toxin catalytic domain delivery to the eukaryotic cell cytosol and the cellular factors that directly participate in the process. *Toxins (Basel)*, 3, 294-308. [↗](#)

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

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Editions

2014-03-05	Authored, Edited	D'Eustachio, P.
2014-11-19	Reviewed	Liu, S.

DT A:B binds HBEGF and CD9 on the target cell surface ↗

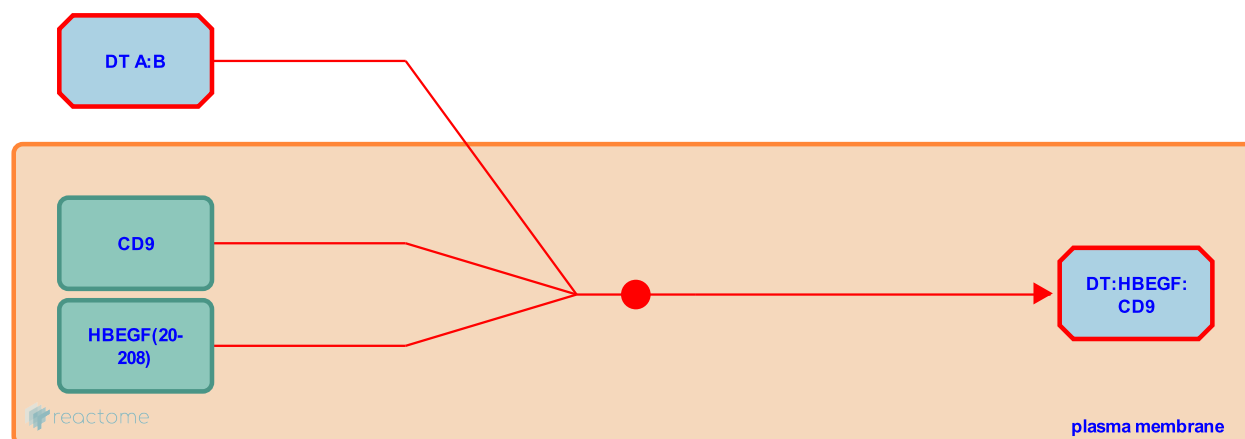
Location: [Uptake and function of diphtheria toxin](#)

Stable identifier: R-HSA-5336417

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: diphtheria



Diphtheria toxin fragments A and B, linked by a disulfide bond (DT A:B) (Collier and Kandel 1971; DeLange et al. 1979; Lambotte et al. 1980; Michel et al. 1972) bind to molecules of proheparin-binding EGF-like growth factor (HBEGF) and CD9 antigen on the target cell plasma membrane. While binding to HBEGF is sufficient for DT A:B uptake into a target cell, presence of CD9 on the target cell surface substantially increases its sensitivity to DT and cross-linking and immunoprecipitation studies indicate that DT A:B, HBEGF, and CD9 form a complex on the cell surface (Brown et al. 1993; Iwamoto et al. 1994). The organization and order of assembly of the complex are not known.

Followed by: [Clathrin-mediated endocytosis of DT:HBEGF:CD9](#)

Literature references

- Collier, RJ., Kandel, J. (1971). Structure and activity of diphtheria toxin. I. Thiol-dependent dissociation of a fraction of toxin into enzymically active and inactive fragments. *J. Biol. Chem.*, 246, 1496-503. ↗
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- Williams, LC., Collier, RJ., DeLange, RJ., Drazin, RE. (1979). The amino acid sequence of fragment A, an enzymically active fragment of diphtheria toxin. III. The chymotryptic peptides, the peptides derived by cleavage at tryptophan residues, and the complete sequence of the protein. *J. Biol. Chem.*, 254, 5838-42. ↗

Editions

2014-03-05	Authored, Edited	D'Eustachio, P.
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Clathrin-mediated endocytosis of DT:HBEGF:CD9 ↗

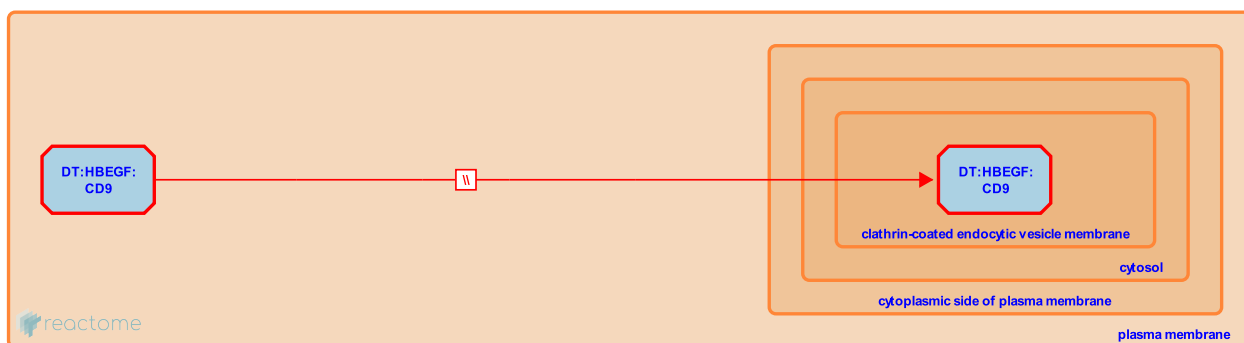
Location: [Uptake and function of diphtheria toxin](#)

Stable identifier: R-HSA-5336422

Type: omitted

Compartments: plasma membrane, clathrin-coated endocytic vesicle membrane

Diseases: diphtheria



The complex of diphtheria toxin (DT A:B) and target cell surface proteins HBEGF and CD9 is taken up by endocytosis into a clathrin-coated vesicle (Moya et al. 1985; Murphy 2011).

Preceded by: [DT A:B binds HBEGF and CD9 on the target cell surface](#)

Followed by: [DT:HBEGF:CD9 is transported from clathrin-coated vesicle to endosome](#)

Literature references

Murphy, JR. (2011). Mechanism of diphtheria toxin catalytic domain delivery to the eukaryotic cell cytosol and the cellular factors that directly participate in the process. *Toxins (Basel)*, 3, 294-308. ↗

Louvard, D., Dautry-Varsat, A., Goud, B., Moya, M., Boquet, P. (1985). Inhibition of coated pit formation in Hep2 cells blocks the cytotoxicity of diphtheria toxin but not that of ricin toxin. *J. Cell Biol.*, 101, 548-59. ↗

Editions

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DT:HBEGF:CD9 is transported from clathrin-coated vesicle to endosome ↗

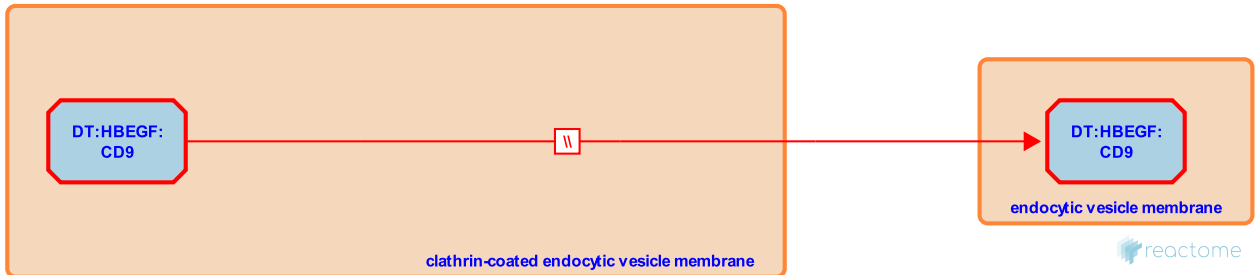
Location: [Uptake and function of diphtheria toxin](#)

Stable identifier: R-HSA-5336413

Type: omitted

Compartment: clathrin-coated endocytic vesicle membrane, endocytic vesicle membrane

Diseases: diphtheria



The target cell clathrin-coated vesicle containing diphtheria toxin (DT A:B) in a complex with target cell proteins HBEGF and CD9 is transformed into an endocytic vesicle (Murphy 2011).

Preceded by: [Clathrin-mediated endocytosis of DT:HBEGF:CD9](#)

Followed by: [DT fragment B transports DT fragment A from target cell endosome membrane](#)

Literature references

Murphy, JR. (2011). Mechanism of diphtheria toxin catalytic domain delivery to the eukaryotic cell cytosol and the cellular factors that directly participate in the process. *Toxins (Basel)*, 3, 294-308. ↗

Editions

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DT fragment B transports DT fragment A from target cell endosome membrane [↗](#)

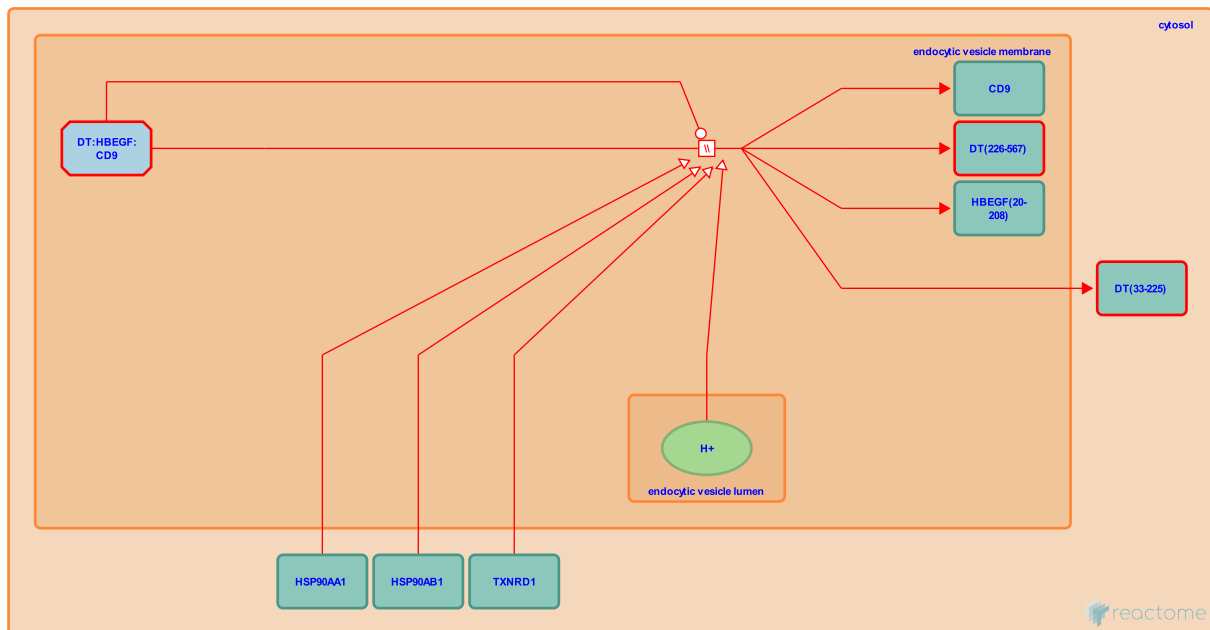
Location: [Uptake and function of diphtheria toxin](#)

Stable identifier: R-HSA-5336420

Type: omitted

Compartments: cytosol, endocytic vesicle membrane

Diseases: diphtheria



The normal process of acidification of the endocytic vesicle containing diphtheria toxin (DT A:B) associated with target cell proteins HBEGF and CD9 is thought to cause a conformational change in the toxin. Its B fragment forms a channel in the endocytic vesicle membrane through which the A fragment is extruded into the target cell cytosol. There, reduction of the disulfide bond connecting the A and B fragments releases the A fragment to refold. The process requires participation of target cell heat shock proteins (HSP90AA1 and HSP90AB1) and thioredoxin reductase 1 (TXNRD1), which may mediate disulfide bond cleavage (Ratts et al. 2003; Murphy 2011).

Preceded by: [DT:HBEGF:CD9 is transported from clathrin-coated vesicle to endosome](#)

Followed by: [DT fragment A ADP-ribosylates target cell EEF](#)

Literature references

Murphy, JR. (2011). Mechanism of diphtheria toxin catalytic domain delivery to the eukaryotic cell cytosol and the cellular factors that directly participate in the process. *Toxins (Basel)*, 3, 294-308. [↗](#)

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Editions

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2014-11-19	Reviewed	Liu, S.

DT fragment A ADP-ribosylates target cell EEF [↗](#)

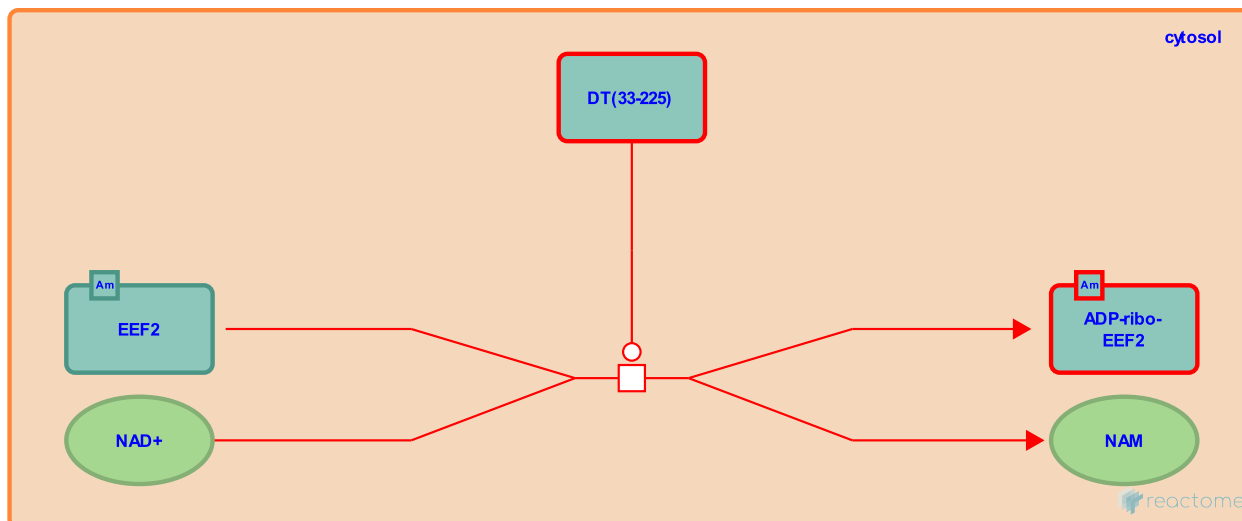
Location: [Uptake and function of diphtheria toxin](#)

Stable identifier: R-HSA-5336421

Type: transition

Compartments: cytosol

Diseases: diphtheria



Target cell elongation factor 2 (EEF2) is ADP-ribosylated in a reaction catalyzed by cytosolic diphtheria toxin fragment A (DT A), inactivating it (Honjo et al. 1971; Van Ness et al. 1980a,b). The loss of EEF2 activity blocks target cell protein synthesis, and a small number of DT A molecules are capable of inactivating sufficient EEF2 to cause target cell death (Collier 1975).

Preceded by: [DT fragment B transports DT fragment A from target cell endosome membrane](#)

Literature references

Howard, JB., Bodley, JW., Van Ness, BG. (1980). ADP-ribosylation of elongation factor 2 by diphtheria toxin. NMR spectra and proposed structures of ribosyl-diphthamide and its hydrolysis products. *J. Biol. Chem.*, 255, 10710-6. [↗](#)

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

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