Protein folding

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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.

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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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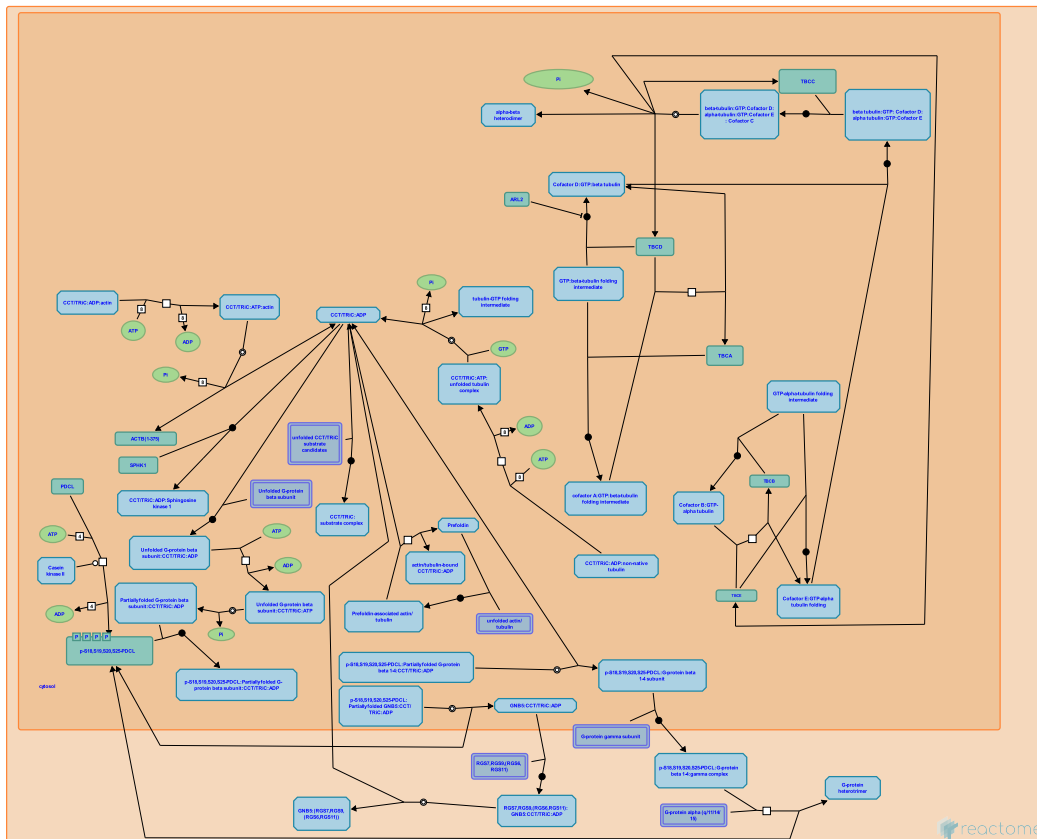
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Protein folding ↗

Stable identifier: R-HSA-391251

Compartments: cytosol

Due to the crowded envirnoment within the cell, many proteins must interact with molecular chaperones to attain their native conformation (reviewed in Young et al., 2004). Chaperones recognize and associate with proteins in their non-native state and facilitate their folding by stabilizing the conformation of productive folding intermediates. Chaperones that take part broadly in de novo protein folding, such as the Hsp70s and the chaperonins, facilitate the folding process through cycles of substrate binding and release regulated by their ATPase activity (see Young et al., 2004; Spiess et al., 2004; Bigotti and Clarke, 2008).

Literature references

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Meyer, AS., Reissmann, S., Frydman, J., Spiess, C. (2004). Mechanism of the eukaryotic chaperonin: protein folding in the chamber of secrets. *Trends Cell Biol, 14,* 598-604. ↗
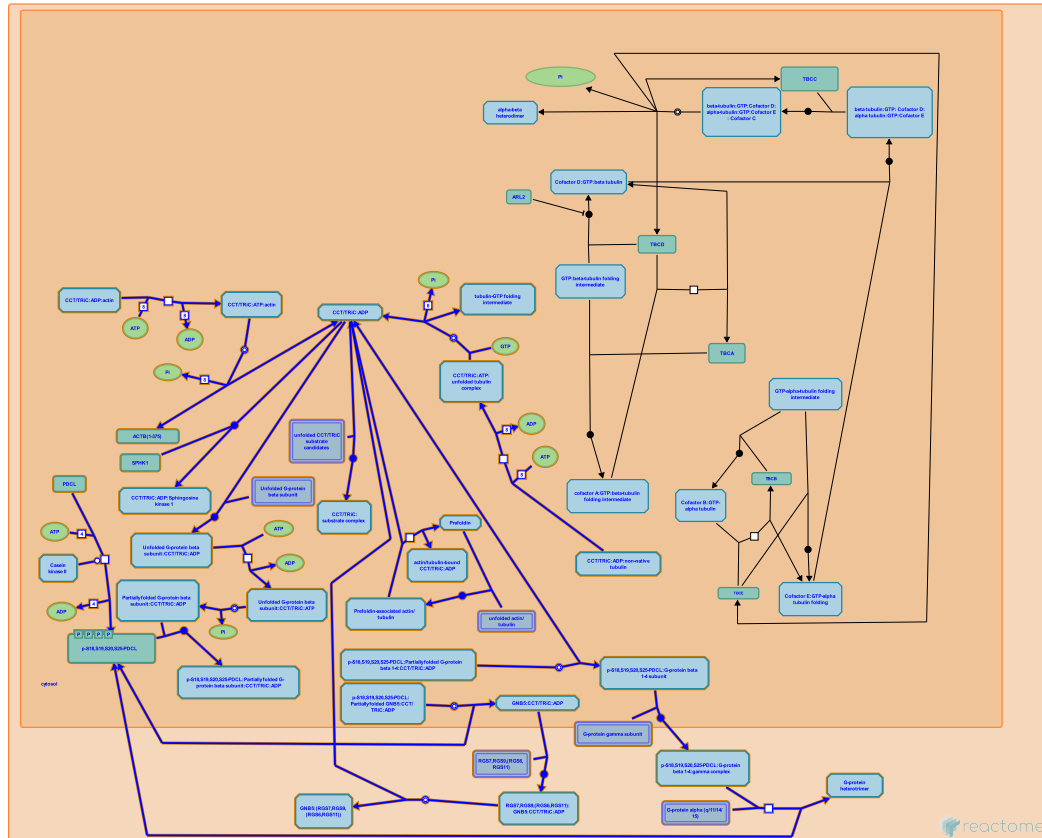
Editions

2008-12-01	Authored	Matthews, L.
2009-01-21	Reviewed	Cowan, NJ.
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Chaperonin-mediated protein folding ↗

Location: Protein folding

Stable identifier: R-HSA-390466

Compartments: cytosol

The eukaryotic chaperonin TCP-1 ring complex (TRiC/ CCT) plays an essential role in the folding of a subset of proteins prominent among which are the actins and tubulins (reviewed in Altschuler and Willison, 2008). CCT/TRiC is an example of a type II chaperonin, defined (in contrast to type I) as functioning in the absence of a cochaperonin. TriC/CCT is a multisubunit toroidal complex that forms a cylinder containing two back-to-back stacked rings enclosing a cavity where substrate folding occurs in an ATP dependent process (reviewed in Altschuler and Willison, 2008). CCT/TriC contains eight paralogous subunits that are conserved throughout eukaryotic organisms (Leroux and Hartl 2000; Archibald et al. 2001; Valpuesta et al. 2002). CCT-mediated folding of non-native substrate protein involves capture through hydrophobic contacts with multiple chaperonin subunits followed by transfer of the protein into the central ring cavity where it folds. Although folding is initiated within this central cavity, only 5%-20% of proteins that are released have partitioned to the native state. The remaining portion is then recaptured by other chaperonin molecules (Cowan and Lewis 2001). This cycling process may be repeated multiple times before a target protein partitions to the native state. In the cell, binding to CCT occurs via presentation of target protein bound to upstream chaperones. During translation, the emerging polypeptide chain may be transferred from the ribosome to CCT via the chaperone Prefoldin (Vainberg et al., 1998) or the Hsp70 chaperone machinery (Melville et al., 2003). While the majority of CCT substrates ultimately partition to the native state as soluble, monomeric proteins, alpha and beta tubulin are unusual in that they require additional cofactors that are required to assemble the tubulin heterodimer (Cowan and Lewis 2001).

Literature references

Lewis, SA., Cowan, NJ. (2001). Type II chaperonins, prefoldin, and the tubulin-specific chaperones. *Adv Protein Chem , 59,* 73-104. ↗

Meyer, AS., Reissmann, S., Frydman, J., Spiess, C. (2004). Mechanism of the eukaryotic chaperonin: protein folding in the chamber of secrets. *Trends Cell Biol, 14,* 598-604. ↗
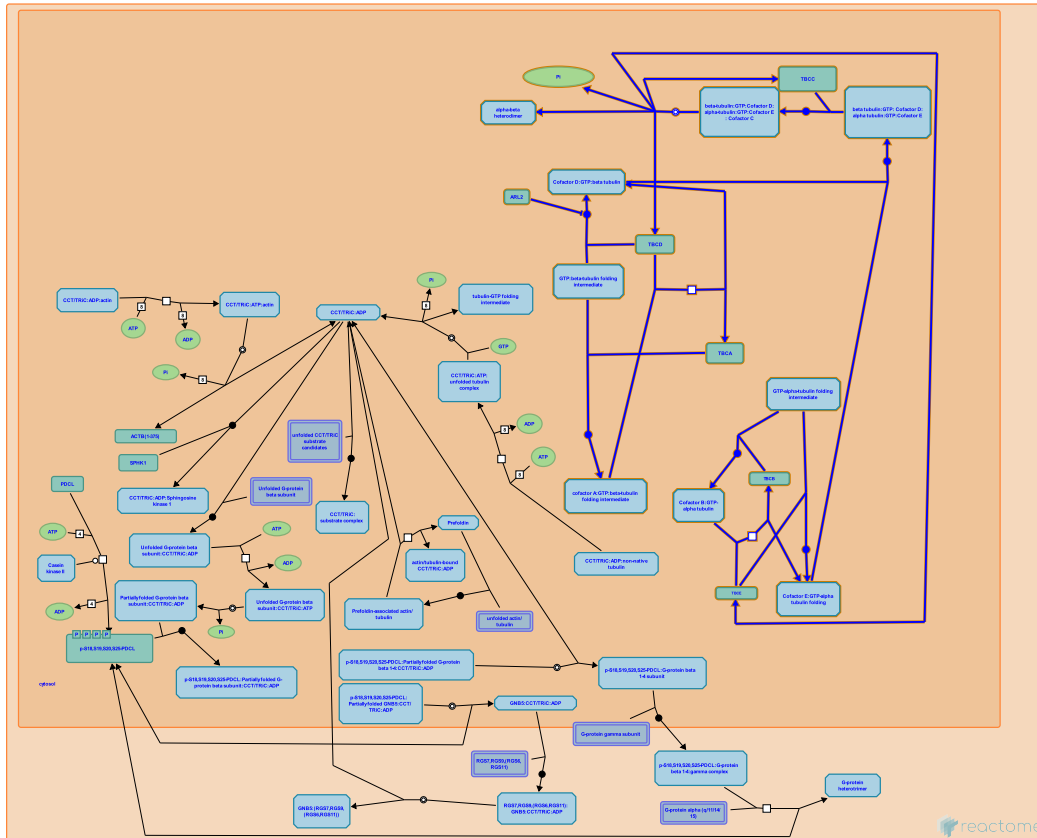
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Post-chaperonin tubulin folding pathway ↗

Location: Protein folding

Stable identifier: R-HSA-389977

Compartments: cytosol

Alpha and beta tubulin folding intermediates are formed through ATP-dependent interaction with TriC/CCT. In order to form a functional heterodimer, these folding intermediates undergo a series of interactions with five proteins: (cofactors A-E) following release from TriC/CCT (reviewed in Cowan and Lewis et al., 2001). These interactions are described in the reactions below. Ultimately, alpha tubulin, when associated with cofactor E, interacts with cofactor D-bound beta-tubulin. The entry of cofactor C into this complex results in the discharge of native heterodimer triggered by GTP hydrolysis in beta tubulin (Tian et al., 1997).

Literature references

Lewis, SA., Cowan, NJ., Tian, G. (1997). The alpha- and beta-tubulin folding pathways. *Trends Cell Biol, 7*, 479-84. ↗

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