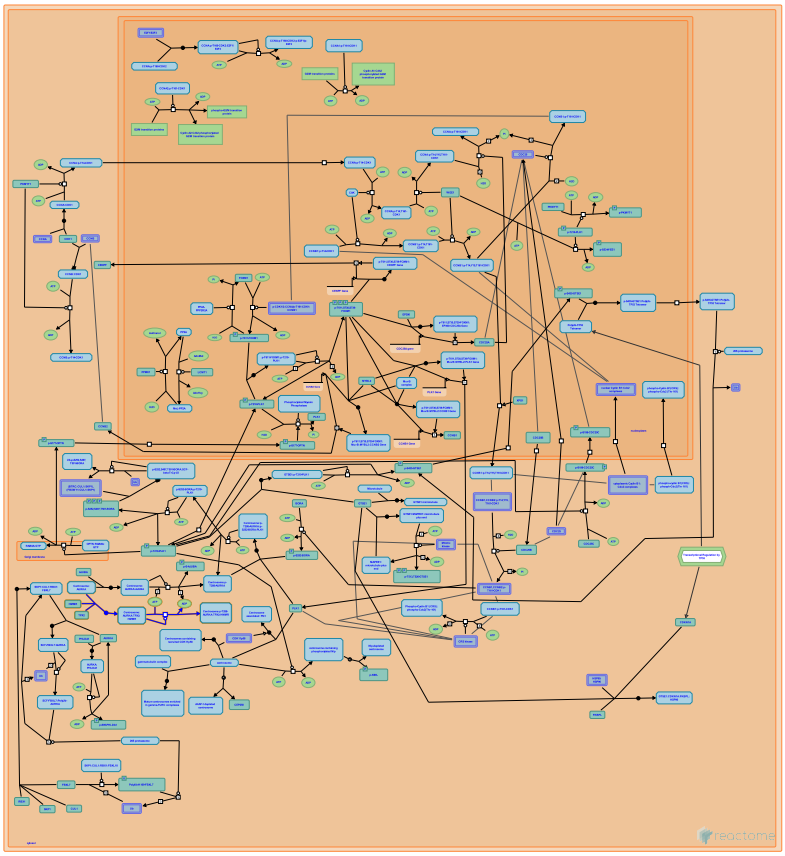
AURKA Activation by TPX2



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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.
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. ↗

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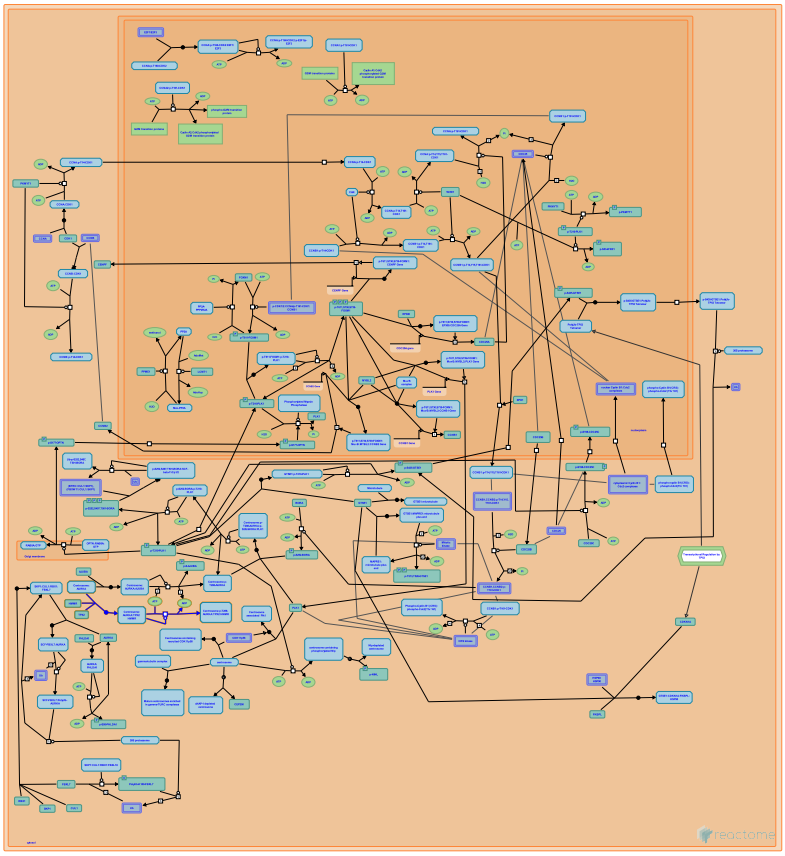
AURKA Activation by TPX2 ↗

Stable identifier: R-HSA-8854518



TPX2 binds to aurora kinase A (AURKA) at centrosomes and promotes its activation by facilitating AURKA active conformation and autophosphorylation of the AURKA threonine residue T288 (Bayliss et al. 2003, Xu et al. 2011, Giubettini et al. 2011, Dodson and Bayliss 2012).

Literature references

Dodson, CA., Bayliss, R. (2012). Activation of Aurora-A kinase by protein partner binding and phosphorylation are independent and synergistic. *J. Biol. Chem., 287*, 1150-7. ↗

Scrofani, J., Asteriti, IA., Lavia, P., Giubettini, M., Lindon, C., De Luca, M. et al. (2011). Control of Aurora-A stability through interaction with TPX2. *J. Cell. Sci., 124*, 113-22. ↗

Sardon, T., Bayliss, R., Conti, E., Vernos, I. (2003). Structural basis of Aurora-A activation by TPX2 at the mitotic spindle. *Mol. Cell, 12*, 851-62. ↗

Li, Y., Wang, X., Wang, Y., Xiao, Z., Xu, X. (2011). Two TPX2-dependent switches control the activity of Aurora A. *PLoS ONE, 6*, e16757. ↗

Editions

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2016-02-16	Reviewed	Maxwell, CA., Chen, H.

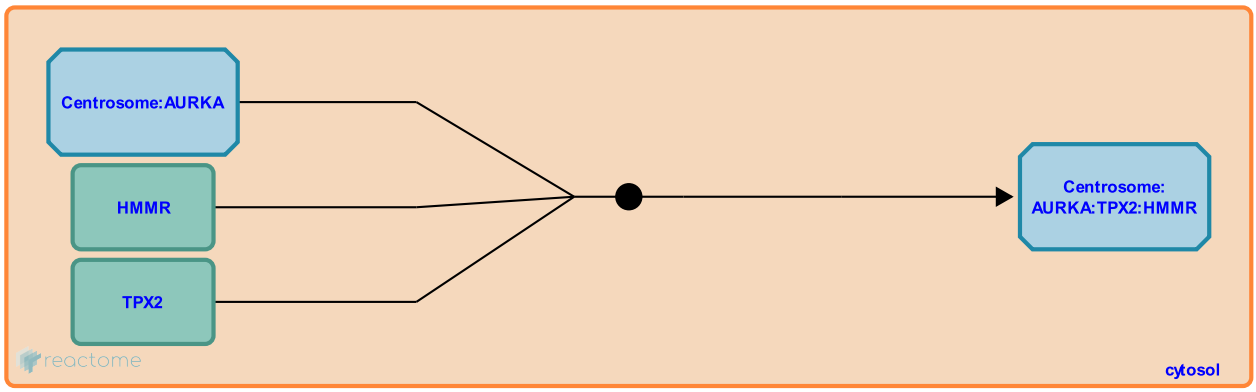
TPX2 binds AURKA at centrosomes ↗

Location: AURKA Activation by TPX2

Stable identifier: R-HSA-8853405

Type: binding

Compartments: cytosol



TPX2 binds to aurora kinase A (AURKA) at centrosomes. The first 43 amino acids at the N-terminus of TPX2 are needed for binding to AURKA (Bayliss et al. 2003). HMMR (RHAMM) binds to TPX2 (Groen et al. 2004, Maxwell et al. 2005) and is involved in the proper localization of TPX2 to centrosomes and TPX2-mediated AURKA activation (Chen et al. 2014, Scrofani et al. 2015).

TPX2 binding to Aurora A protects premature AURKA degradation by APC/C-mediated proteolysis during early mitosis. TPX2 differentially regulates AURKA stability, activity and localization. While amino acids 1-43 in TPX2 facilitate complex formation between AURKA and TPX2 and promote kinase activation, they are insufficient for AURKA targeting to the mitotic spindle (Giubettini et al. 2011).

Followed by: TPX2 promotes AURKA autophosphorylation

Literature references

Groen, AC., Coughlin, M., Ohi, R., Mitchison, TJ., Cameron, LA., Miyamoto, DT. (2004). XRHAMM functions in ran-dependent microtubule nucleation and pole formation during anastral spindle assembly. *Curr. Biol., 14*, 1801-11. ↗

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Sardon, T., Scrofani, J., Vernos, I., Meunier, S. (2015). Microtubule nucleation in mitosis by a RanGTP-dependent protein complex. *Curr. Biol., 25*, 131-40. ↗

Sardon, T., Bayliss, R., Conti, E., Vernos, I. (2003). Structural basis of Aurora-A activation by TPX2 at the mitotic spindle. *Mol. Cell, 12*, 851-62. ↗

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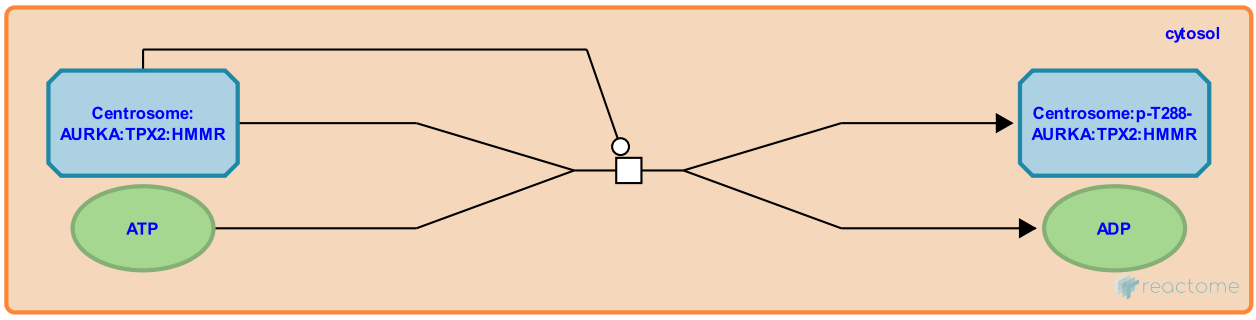
TPX2 promotes AURKA autophosphorylation ↗

Location: AURKA Activation by TPX2

Stable identifier: R-HSA-8853419

Type: transition

Compartments: cytosol



TPX2 promotes aurora kinase A (AURKA) activation via autophosphorylation of AURKA on threonine residue T288. Continuous association of TPX2 with AURKA facilitates active state conformation of AURKA and may prevent inactivation of AURKA by protein phosphatases (Bayliss et al. 2003).

Molecular dynamic simulations suggest the existence of two TPX2-dependent switches for Aurora A activation. 1) TPX2 binding to Aurora A forces lysine residue K143 of AURKA into an “open” state, which pulls ADP out of the ATP binding site in AURKA to promote kinase activation. 2) Arginine residue R180 of AURKA undergoes a “closed” movement upon TPX2 binding, thus capturing phosphorylated threonine T288 of AURKA into a buried position and locking AURKA in its active conformation. The existence of two TPX2-dependent switches in AURKA activation was further verified by the analysis of two AURKA mutants (K143A and R180A) (Xu et al. 2011).AURKA activation is enabled through phosphorylation and TPX2 binding; these two activating switches act synergistically and withough a predefined order (Dodson and Bayliss 2012).

Preceded by: TPX2 binds AURKA at centrosomes

Literature references

Dodson, CA., Bayliss, R. (2012). Activation of Aurora-A kinase by protein partner binding and phosphorylation are independent and synergistic. *J. Biol. Chem., 287*, 1150-7. ↗

Sardon, T., Bayliss, R., Conti, E., Vernos, I. (2003). Structural basis of Aurora-A activation by TPX2 at the mitotic spindle. *Mol. Cell, 12*, 851-62. ↗

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Table of Contents