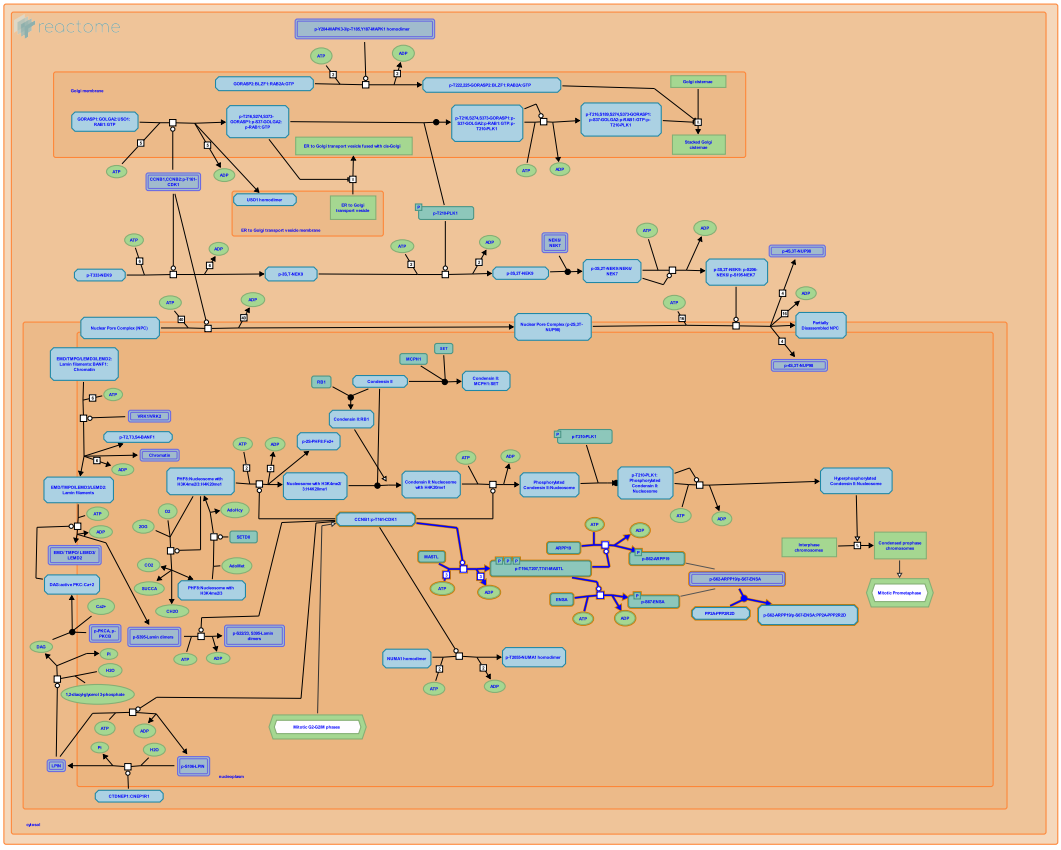
MASTL Facilitates Mitotic Progression



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02/05/2024

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.
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. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

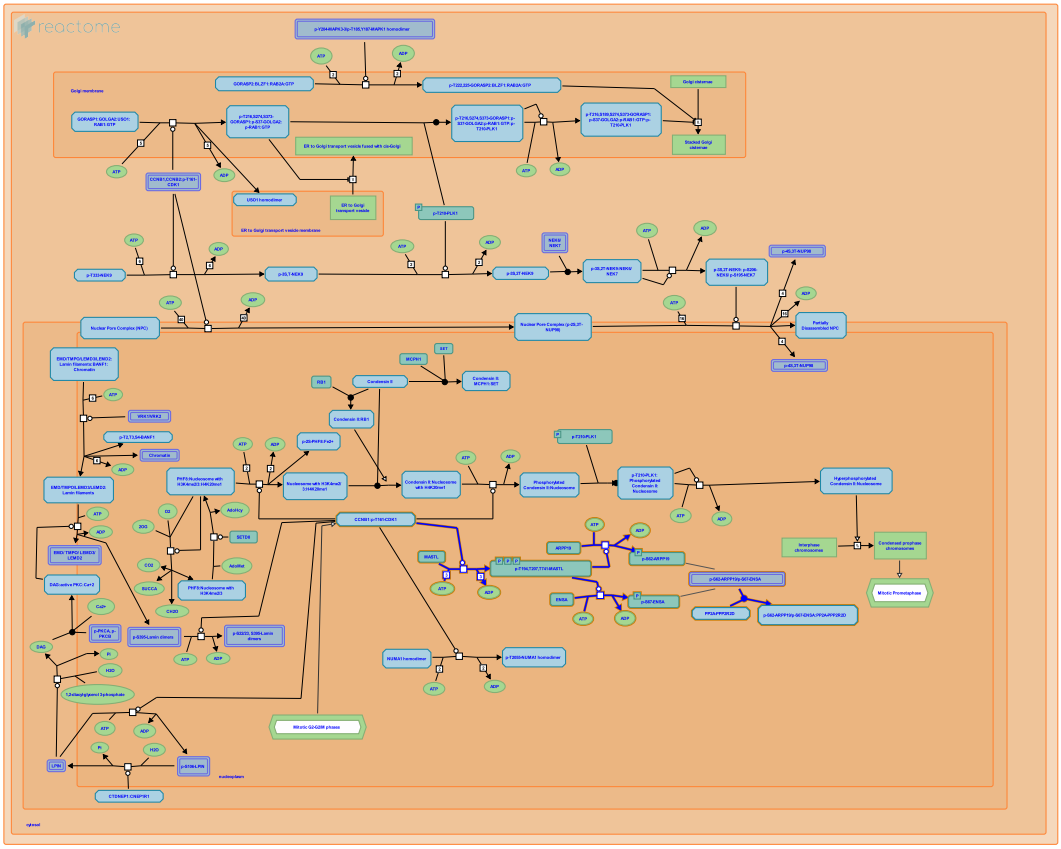
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

MASTL Facilitates Mitotic Progression ↗

Stable identifier: R-HSA-2465910

Compartments: nucleoplasm



The activity of MASTL, also known as the Greatwall kinase (GWL), is necessary for the entry and progression of mitosis. MASTL is activated by phosphorylation of several key residues during mitotic entry. Phosphorylation on the serine residue S875 (S883 in Xenopus), likely through autophosphorylation (Blake-Hodek et al. 2012) appears to be critical (Vigneron et al. 2011). Several other sites, including putative CDK1 targets T194, T207 and T741, contribute to the full activation of MASTL (Yu et al. 2006, Blake-Hodek et al. 2012). Other kinases, such as PLK1 (Vigneron et al. 2011) and other MASTL phosphorylation sites may also be functionally important (Yu et al. 2006, Blake-Hodek et al. 2012).

Activated MASTL phosphorylates ARPP19 and ENSA on serines S62 and S67, respectively, enabling them to bind to and inhibit the phosphatase activity of PP2A complexed with the regulatory subunit PPP2R2D (B55-delta). Inhibition of PP2A-PPP2R2D activity by ARPP19 or ENSA prevents dephosphorylation of CDK1 targets, hence allowing entry and maintenance of mitosis (Mochida et al. 2010, Gharbi-Ayachi et al. 2010, Burgess et al. 2010).

Literature references

Skehel, M., Mochida, S., Hunt, T., Maslen, SL. (2010). Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. *Science, 330*, 1670-3. ↗

Yu, J., Li, Z., Goldberg, ML., Galas, S., Zhao, Y. (2006). Greatwall kinase participates in the Cdc2 autoregulatory loop in Xenopus egg extracts. *Mol. Cell, 22*, 83-91. ↗

Lorca, T., Burgess, A., Van-Dorsselaer, A., Vigneron, S., Strub, JM., Gharbi-Ayachi, A. et al. (2010). The substrate of Greatwall kinase, Arpp19, controls mitosis by inhibiting protein phosphatase 2A. *Science, 330*, 1673-7. ↗

Lorca, T., Burgess, A., Vigneron, S., Raymond, AA., Gharbi-Ayachi, A., Castro, A. et al. (2011). Characterization of the mechanisms controlling Greatwall activity. *Mol. Cell. Biol., 31*, 2262-75. ↗

Chen, W., Castilho, PV., Williams, BC., Mao, Y., Goldberg, ML., Blake-Hodek, KA. et al. (2012). Determinants for activation of the atypical AGC kinase Greatwall during M phase entry. *Mol. Cell. Biol., 32*, 1337-53. ↗

Editions

2012-09-04	Authored	Orlic-Milacic, M.
2012-09-14	Edited	Gillespie, ME.
2012-09-26	Reviewed	Mochida, S.
2012-09-28	Reviewed	Burgess, A.

CDK1 phosphorylates MASTL ↗

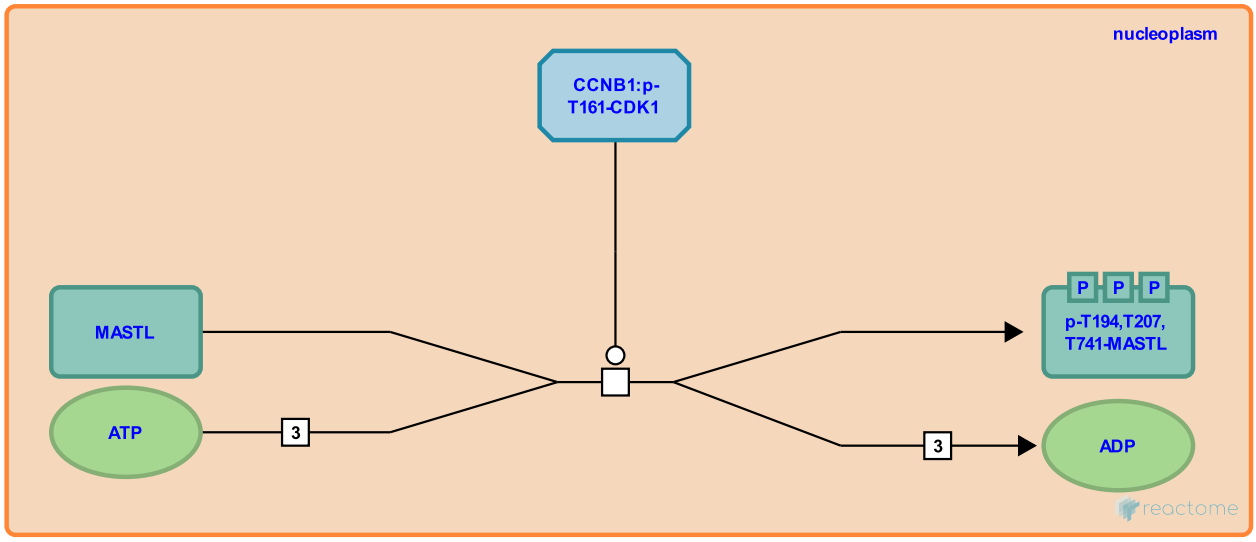
Location: MASTL Facilitates Mitotic Progression

Stable identifier: R-HSA-2430533

Type: transition

Compartments: nucleoplasm

Inferred from: CDK1 phosphorylates Mastl (Homo sapiens)



At the beginning of mitosis, MASTL (GWL, Greatwall kinase) is activated by phosphorylation at several key sites. Many of these sites, including functionally important threonine residues T194, T207 and T741 (corresponding to Xenopus residues T193, T206 and T748), are proline directed, matching CDK1 consensus sequence, and thus probably phosphorylated by CDK1, as shown by in vitro studies (Yu et al. 2006. Blake-Hodek et al. 2012). Phosphorylation of the serine residue S875 (S883 in Xenopus) is implicated as critical for the mitotic function of MASTL (Vigneron et al. 2011) and likely occurs through autophosphorylation (Blake-Hodek et al. 2012). Other kinases, such as PLK1 (Vigneron et al. 2011) and other MASTL phosphorylation sites may also be involved in mitotic activation of MASTL (Yu et al. 2006, Vigneron et al. 2011, Blake-Hodek et al. 2012). Phosphorylation of the serine residue S102 (S101 in Xenopus) is functionally important but the responsible kinase has not been identified (Blake-Hodek et al. 2012).

Followed by: MASTL phosphorylates ENSA, MASTL (GWL) phosphorylates ARPP19

Literature references

Yu, J., Li, Z., Goldberg, ML., Galas, S., Zhao, Y. (2006). Greatwall kinase participates in the Cdc2 autoregulatory loop in Xenopus egg extracts. *Mol. Cell, 22*, 83-91. ↗

Lorca, T., Burgess, A., Vigneron, S., Raymond, AA., Gharbi-Ayachi, A., Castro, A. et al. (2011). Characterization of the mechanisms controlling Greatwall activity. *Mol. Cell. Biol., 31*, 2262-75. ↗

Chen, W., Castilho, PV., Williams, BC., Mao, Y., Goldberg, ML., Blake-Hodek, KA. et al. (2012). Determinants for activation of the atypical AGC kinase Greatwall during M phase entry. *Mol. Cell. Biol., 32*, 1337-53. ↗

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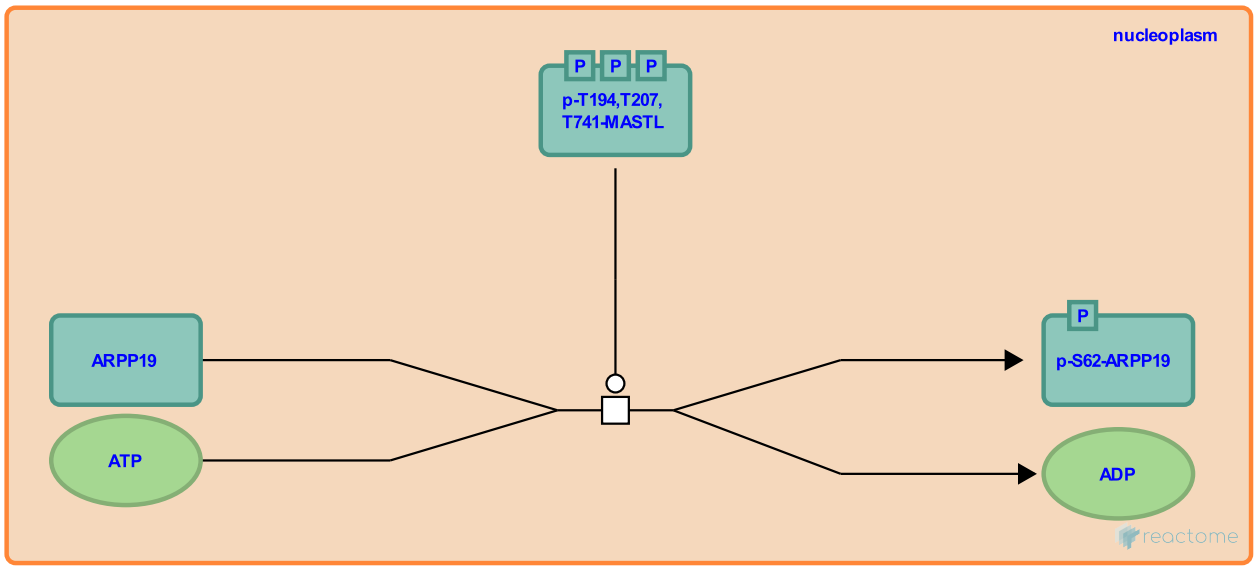
MASTL (GWL) phosphorylates ARPP19 ↗

Location: MASTL Facilitates Mitotic Progression

Stable identifier: R-HSA-2168079

Type: transition

Compartments: nucleoplasm



MASTL (GWL i.e. Greatwall kinase) phosphorylates ARPP19 on serine residue S62 (Gharbi-Ayachi et al. 2010). S62 of human ARPP19 corresponds to serine residue S67 of Xenopus Arpp19, which is phosphorylated by Xenopus Mastl (Mochida et al. 2010).

Preceded by: CDK1 phosphorylates MASTL

Followed by: p-S62-ARPP19/p-S67-ENSA binds PP2A-PPP2R2D

Literature references

Skehel, M., Mochida, S., Hunt, T., Maslen, SL. (2010). Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. *Science, 330*, 1670-3. ↗

Lorca, T., Burgess, A., Van-Dorsselaer, A., Vigneron, S., Strub, JM., Gharbi-Ayachi, A. et al. (2010). The substrate of Greatwall kinase, Arpp19, controls mitosis by inhibiting protein phosphatase 2A. *Science, 330*, 1673-7. ↗

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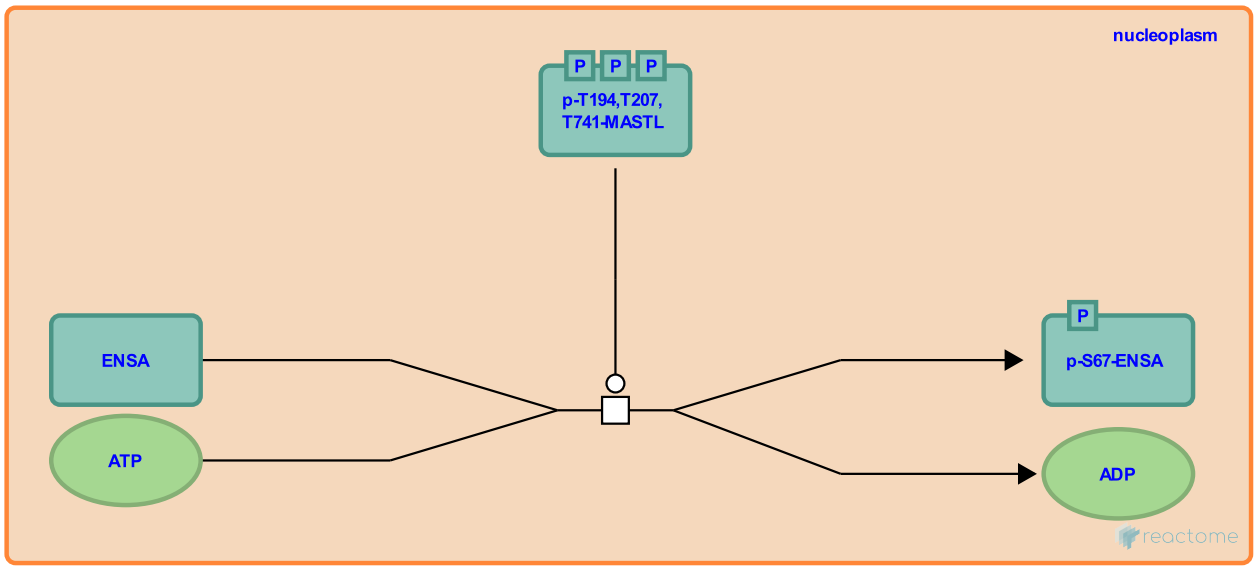
MASTL phosphorylates ENSA ↗

Location: MASTL Facilitates Mitotic Progression

Stable identifier: R-HSA-2430535

Type: transition

Compartments: nucleoplasm



MASTL (GWL) activates ENSA by phosphorylating it on serine residue S67 (Mochida et al. 2010, Gharbi-Ayachi et al. 2010).

Preceded by: CDK1 phosphorylates MASTL

Followed by: p-S62-ARPP19/p-S67-ENSA binds PP2A-PPP2R2D

Literature references

Skehel, M., Mochida, S., Hunt, T., Maslen, SL. (2010). Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. *Science, 330*, 1670-3. ↗

Lorca, T., Burgess, A., Van-Dorsselaer, A., Vigneron, S., Strub, JM., Gharbi-Ayachi, A. et al. (2010). The substrate of Greatwall kinase, Arpp19, controls mitosis by inhibiting protein phosphatase 2A. *Science, 330*, 1673-7. ↗

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p-S62-ARPP19/p-S67-ENSA binds PP2A-PPP2R2D ↗

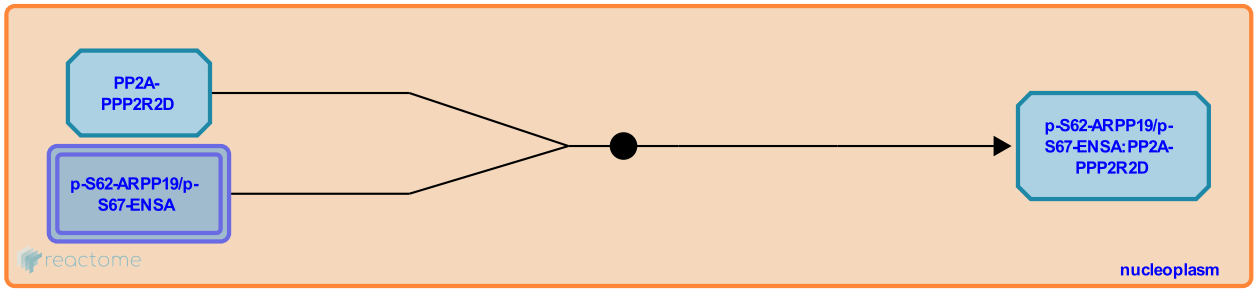
Location: MASTL Facilitates Mitotic Progression

Stable identifier: R-HSA-2430552

Type: binding

Compartments: nucleoplasm

Inferred from: p-S67-Ensa/p-S67-Arpp19 binds PP2A-Ppp2r2d (Xenopus laevis)



ARPP19 and ENSA, activated by MASTL (GWL) mediated phosphorylation, bind and inhibit PP2A complexed with the regulatory subunit PPP2R2D (B55-delta). Inhibition of PP2A-PPP2R2D phosphatase activity allows mitotis entry and mainetance by preventing dephosphorylation of CDK1 mitotic targets (Mochida et al. 2010, Gharbi-Ayachi et al. 2010).

Preceded by: MASTL (GWL) phosphorylates ARPP19, MASTL phosphorylates ENSA

Literature references

Skehel, M., Mochida, S., Hunt, T., Maslen, SL. (2010). Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. *Science, 330*, 1670-3. ↗

Lorca, T., Burgess, A., Van-Dorsselaer, A., Vigneron, S., Strub, JM., Gharbi-Ayachi, A. et al. (2010). The substrate of Greatwall kinase, Arpp19, controls mitosis by inhibiting protein phosphatase 2A. *Science, 330*, 1673-7. ↗

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