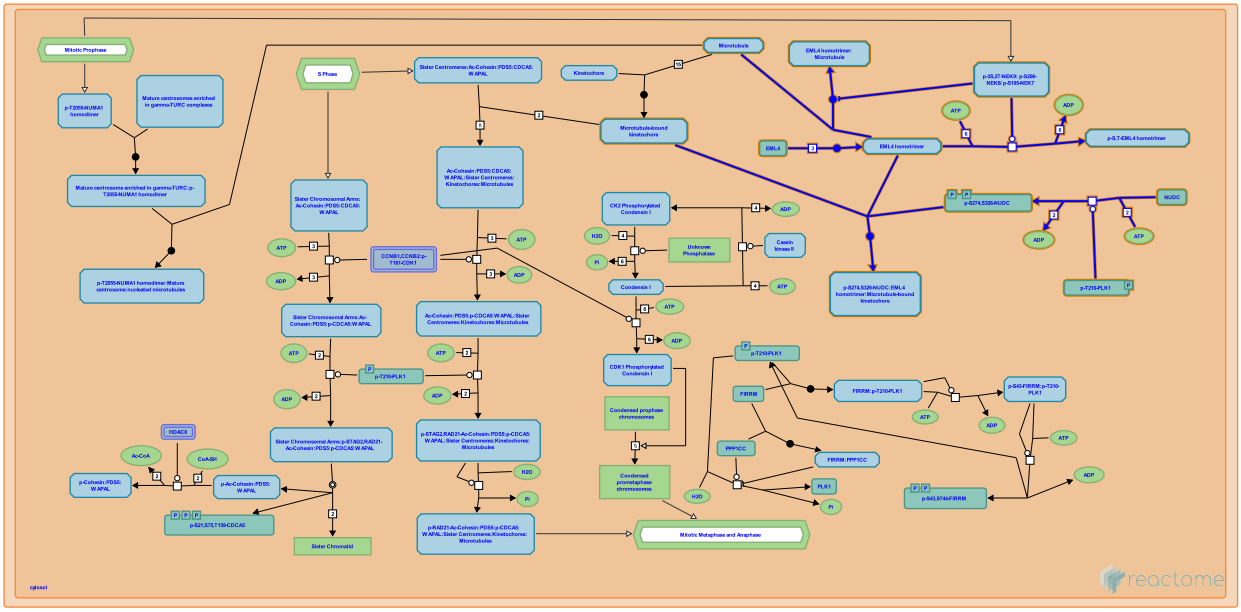
EML4 and NUDC in mitotic spindle formation



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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. ↗

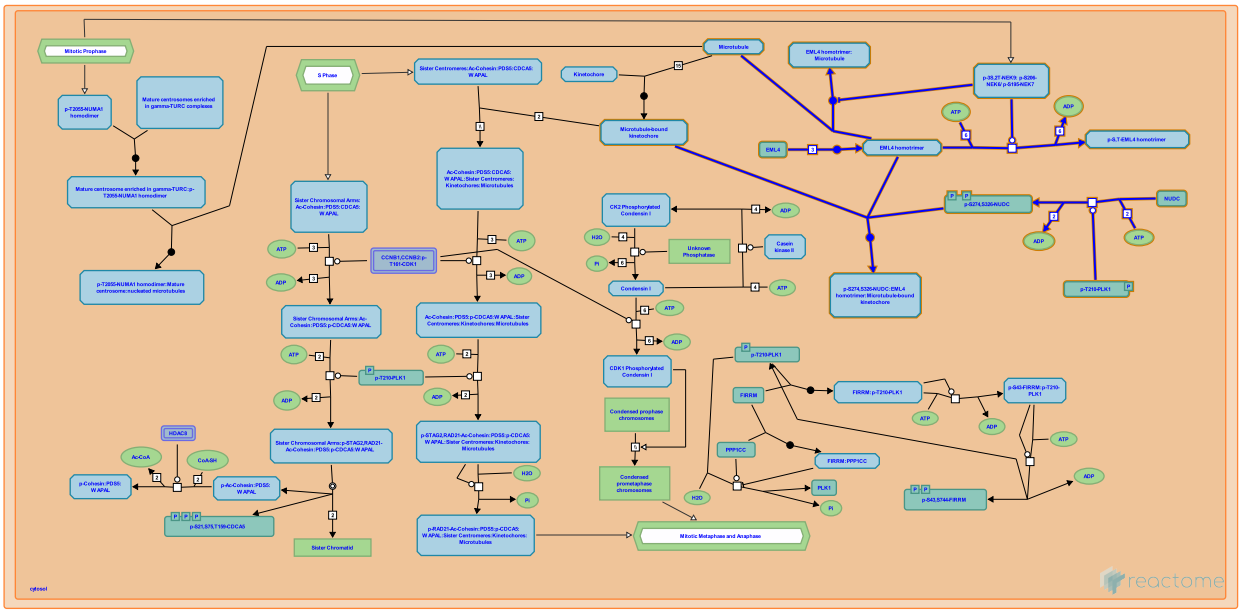
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

EML4 and NUDC in mitotic spindle formation ↗

Stable identifier: R-HSA-9648025



EML4 and NUDC proteins are required for mitotic spindle formation, attachment of spindle microtubule ends to kinetochores, and alignment of mitotic chromosome at the metaphase plate. EML4 is a WD40 family protein that binds to interphase microtubules and stabilizes them (Houtman et al. 2007, Adib et al. 2019). At mitotic entry, EML4 undergoes phosphorylation (Pollmann et al. 2006, Adib et al. 2019) by serine/threonine kinases NEK6 and NEK7, leading to its dissociation from microtubules, which is necessary for the assembly of a dynamic mitotic spindle (Adib et al. 2019). EML4, through its WD40 repeats, interacts with NUDC and recruits it to the kinetochores of the mitotic spindle (Chen et al. 2015). It is possible that other mitotic kinases, besides NEK6 and NEK7, also phosphorylate EML4. Phosphorylation of different residues of EML4 could reduce or increase affinity of EML4 for specific subpopulations of microtubules in mitosis.
A recurrent genomic rearrangement, reported in about 5% cases of non-small cell lung cancer (NSCLC) fuses the N-terminal portion of EML4 with the C-terminal portion of ALK (anaplastic lymphoma kinase), resulting in a constitutively active ALK (Soda et al. 2007, Richards et al. 2015).

Literature references

Ishikawa, Y., Watanabe, H., Hatanaka, H., Soda, M., Sugiyama, Y., Takada, S. et al. (2007). Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature, 448*, 561-6. ↗

O'Regan, L., Richards, MW., Bayliss, R., Fry, AM., Straube, A., Montgomery, JM. et al. (2015). Microtubule association of EML proteins and the EML4-ALK variant 3 oncoprotein require an N-terminal trimerization domain. *Biochem. J., 467*, 529-36. ↗

Hyodo, T., Ito, S., Chen, D., Yuan, H., Hamaguchi, M., Kadomatsu, K. et al. (2015). EML4 promotes the loading of NUDC to the spindle for mitotic progression. *Cell Cycle, 14*, 1529-39. ↗

De Zeeuw, CI., Houtman, SH., Rutteman, M., French, PJ. (2007). Echinoderm microtubule-associated protein like protein 4, a member of the echinoderm microtubule-associated protein family, stabilizes microtubules. *Neuroscience, 144*, 1373-82. ↗

O'Regan, L., Atherton, J., Straatman, KR., Richards, MW., Bayliss, R., Fry, AM. et al. (2019). Mitotic phosphorylation by NEK6 and NEK7 reduces the microtubule affinity of EML4 to promote chromosome congression. *Sci Signal, 12* . ↗

Editions

2019-06-25	Authored	Orlic-Milacic, M.
2019-09-30	Reviewed	O'Regan, L., Fry, AM., Lucken, KJ.
2019-10-03	Reviewed	Bechstedt, S.
2019-10-07	Edited	Orlic-Milacic, M.

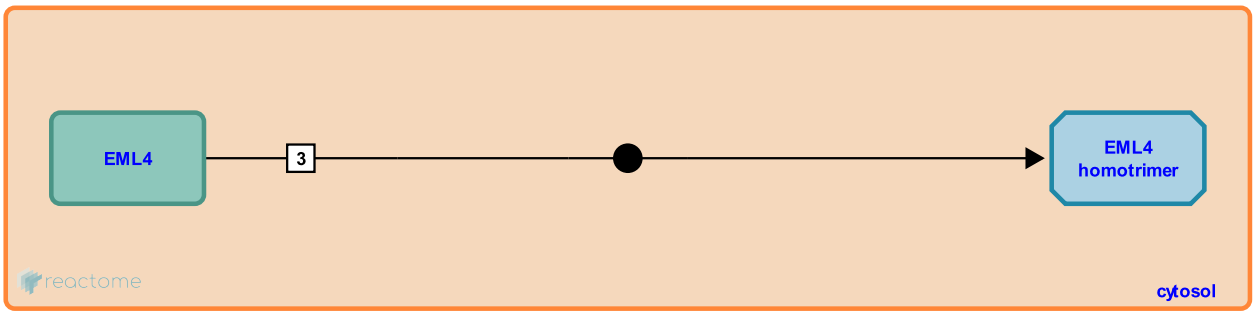
EML4 trimerizes ↗

Location: EML4 and NUDC in mitotic spindle formation

Stable identifier: R-HSA-9647746

Type: binding

Compartments: cytosol



EML4, a microtubule binding protein involved in mitotic spindle formation, forms homotrimers. Trimerization involves the trimerization domain (TD) and the basic region of EML4 and is necessary for its association with the microtubules (Richards et al. 2015). Heterotrimerization of EML4 with other EML family members has not been examined.

Followed by: NEK6 and NEK7 phosphorylate EML4, EML4 binds to microtubules, EML4 recruits NUDC to mitotic spindle

Literature references

O'Regan, L., Richards, MW., Bayliss, R., Fry, AM., Straube, A., Montgomery, JM. et al. (2015). Microtubule association of EML proteins and the EML4-ALK variant 3 oncoprotein require an N-terminal trimerization domain. *Biochem. J., 467,* 529-36. ↗

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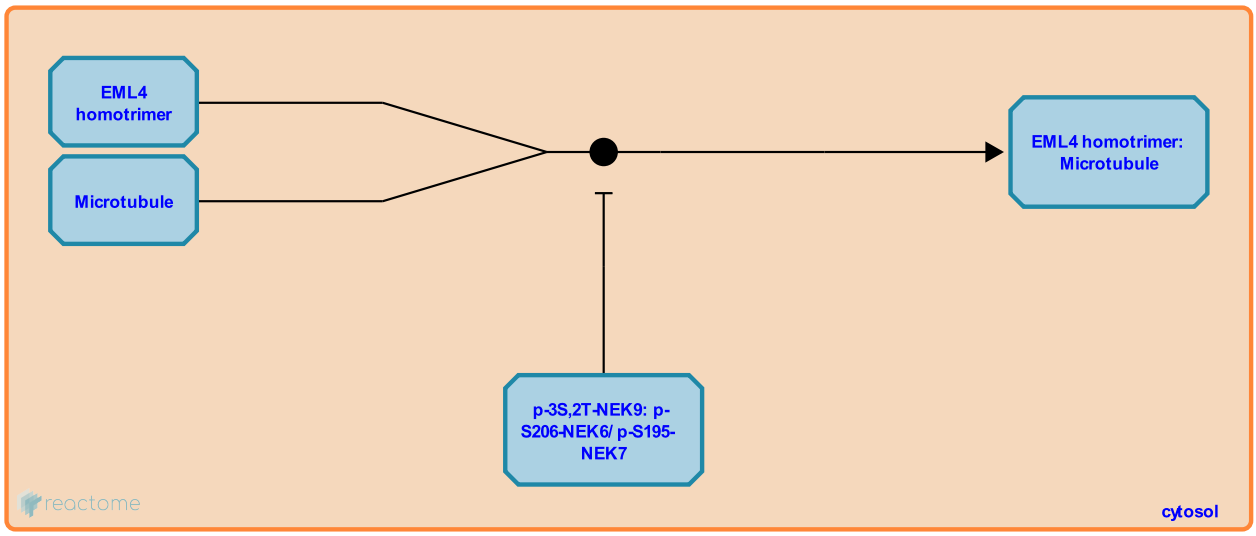
EML4 binds to microtubules ↗

Location: EML4 and NUDC in mitotic spindle formation

Stable identifier: R-HSA-9648017

Type: binding

Compartments: cytosol



In interphase cells, EML4 associates with cytosolic microtubules. The interaction involves the N-terminal domain of EML4 (Pollmann et al. 2006). EML4 trimerization is needed for microtubule binding (Richards et al. 2015). EML4 binding stabilizes interphase microtubules (Houtman et al. 2007, Adib et al. 2019).

Preceded by: EML4 trimerizes

Literature references

O'Regan, L., Richards, MW., Bayliss, R., Fry, AM., Straube, A., Montgomery, JM. et al. (2015). Microtubule association of EML proteins and the EML4-ALK variant 3 oncoprotein require an N-terminal trimerization domain. *Biochem. J., 467*, 529-36. ↗

De Zeeuw, CI., Houtman, SH., Rutteman, M., French, PJ. (2007). Echinoderm microtubule-associated protein like protein 4, a member of the echinoderm microtubule-associated protein family, stabilizes microtubules. *Neuroscience, 144*, 1373-82. ↗

O'Regan, L., Atherton, J., Straatman, KR., Richards, MW., Bayliss, R., Fry, AM. et al. (2019). Mitotic phosphorylation by NEK6 and NEK7 reduces the microtubule affinity of EML4 to promote chromosome congression. *Sci Signal, 12* . ↗

Buck, F., Heidebrecht, HJ., Kruse, ML., Pollmann, M., Parwaresch, R., Adam-Klages, S. (2006). Human EML4, a novel member of the EMAP family, is essential for microtubule formation. *Exp. Cell Res., 312*, 3241-51. ↗

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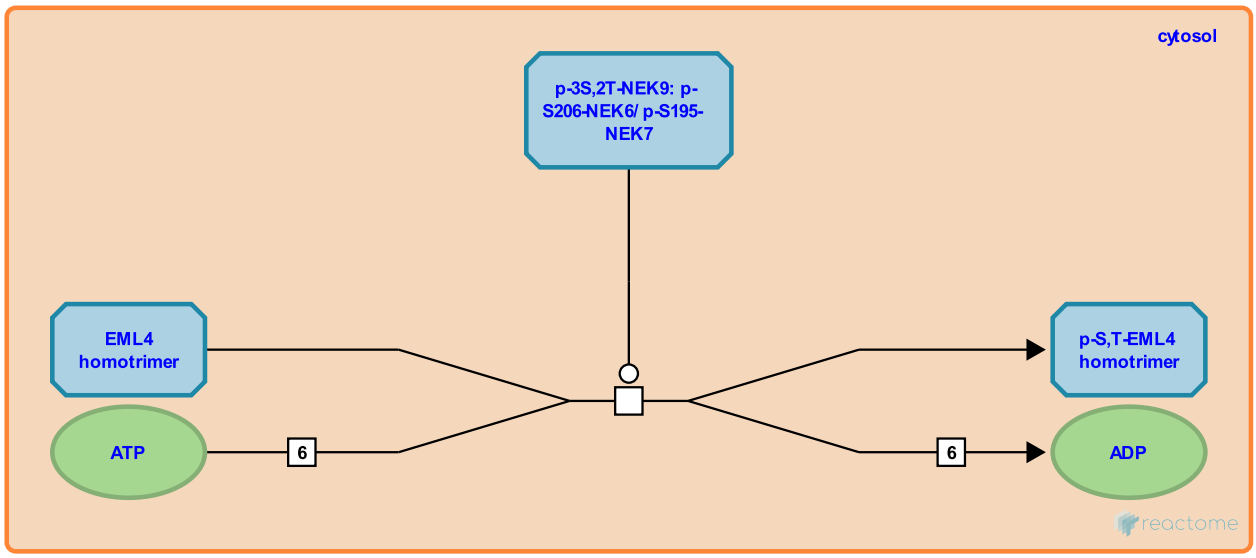
NEK6 and NEK7 phosphorylate EML4 ↗

Location: EML4 and NUDC in mitotic spindle formation

Stable identifier: R-HSA-9648089

Type: transition

Compartments: cytosol



At mitotic entry, EML4 undergoes phosphorylation on serine and/or threonine residues (Pollmann et al. 2006). NEK6 and NEK7 serine/threonine kinases phosphorylate EML4 at evolutionarily conserved serine residues S144 and S146. Phosphorylation of EML4 at S144 and S146 reduces the affinity of EML4 for microtubules, leading to an increase in microtubule instability that is necessary for the assembly of a dynamic mitotic spindle and successful segregation of duplicated chromosomes (Adib et al. 2019).

Preceded by: EML4 trimerizes

Literature references

O'Regan, L., Atherton, J., Straatman, KR., Richards, MW., Bayliss, R., Fry, AM. et al. (2019). Mitotic phosphorylation by NEK6 and NEK7 reduces the microtubule affinity of EML4 to promote chromosome congression. *Sci Signal, 12* . ↗

Buck, F., Heidebrecht, HJ., Kruse, ML., Pollmann, M., Parwaresch, R., Adam-Klages, S. (2006). Human EML4, a novel member of the EMAP family, is essential for microtubule formation. *Exp. Cell Res., 312*, 3241-51. ↗

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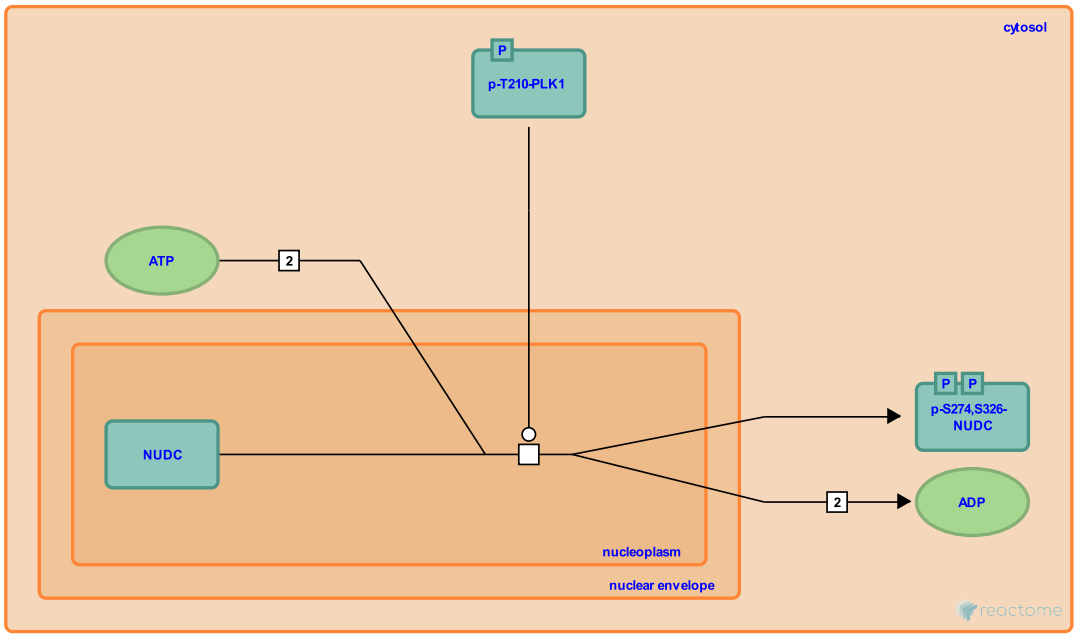
PLK1 phosphorylates NUDC ↗

Location: EML4 and NUDC in mitotic spindle formation

Stable identifier: R-HSA-156682

Type: transition

Compartments: nucleoplasm



The polo-like kinase PLK1 phosphorylates NUDC on serine residues S274 and S326. PLK1-mediated phosphorylation of NUDC is required for both mitotic spindle formation and cytokinesis (Zhou et al. 2003). Interaction of NUDC with dynactin and dynein complexes is also important for its role in mitosis (Aumais et al. 2003). In interphase cells, NUDC is acetylated on lysine residue K39 by an unknown protein acetyl transferase. Deacetylation of NUDC, possibly by HDAC3, at the beginning of mitosis is required for mitotic progression. The interaction of NUDC with PLK1 does not depend on the acetylation status of NUDC (Chuang et al. 2013).

Followed by: EML4 recruits NUDC to mitotic spindle

Literature references

Caldwell, GA., Caldwell, KA., Lin, SH., Luo, W., Aumais, JP., Nishino, M. et al. (2003). Role for NudC, a dynein-associated nuclear movement protein, in mitosis and cytokinesis. *J Cell Sci, 116*, 1991-2003. ↗

Aumais, JP., Liu, X., Zhou, T., Yu-Lee, LY., Erikson, RL. (2003). A role for Plk1 phosphorylation of NudC in cytokinesis. *Dev Cell, 5*, 127-38. ↗

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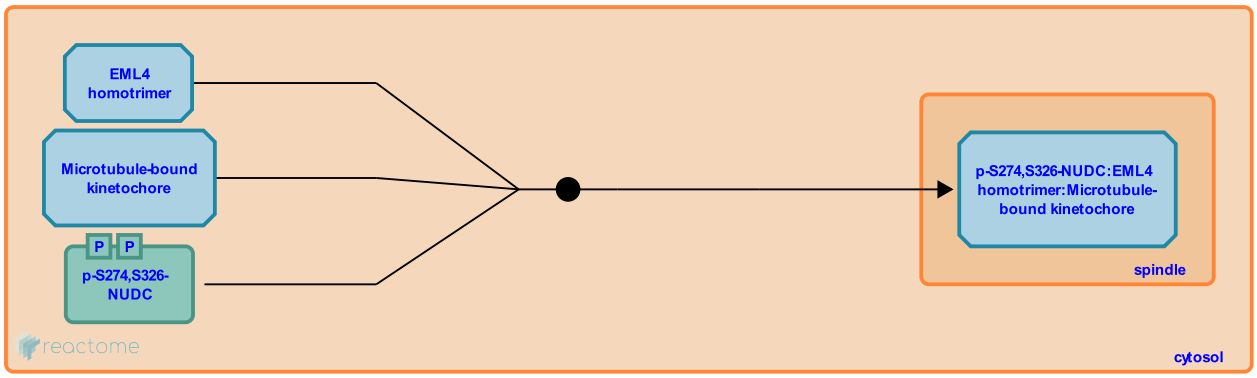
EML4 recruits NUDC to mitotic spindle ↗

Location: EML4 and NUDC in mitotic spindle formation

Stable identifier: R-HSA-9648114

Type: binding

Compartments: cytosol, spindle



EML4 binds to NUDC and recruits it to the kinetochores of the mitotic spindle. The interaction involves the WD40 repeats of EML4 and the C-terminus of NUDC (Chen et al. 2015). Knockdown of EML4 produces similar mitotic defects as the knockdown of NUDC. The knockdown of either of these two genes frequently results in post-mitotic cell death, due to activation of the mitotic spindle checkpoint (Chen et al. 2015, Adib et al. 2019). It is uncertain if PLK1-mediated phosphorylation of NUDC precedes its binding to EML4.

Preceded by: PLK1 phosphorylates NUDC, EML4 trimerizes

Literature references

Hyodo, T., Ito, S., Chen, D., Yuan, H., Hamaguchi, M., Kadomatsu, K. et al. (2015). EML4 promotes the loading of NUDC to the spindle for mitotic progression. *Cell Cycle, 14*, 1529-39. ↗

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Table of Contents